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PATENT & TRADEMARK OFFICE

#36

APPLICANT:	Phillips, J.O.	)	ATTORNEY DOCKET:	01723326
		)		
PATENT NO.:	6,489,346	)	GROUP ART UNIT:	1625
		)		
FILED:	January 11, 2000	)	EXAMINER:	Fan, J.
		)		

TITLE: Substituted Benzimidazole Dosage Forms and Method of Using Same

DATE: August 12, 2004 CUSTOMER NO.: 26565

Certificate of Mailing by "Express Mail"

"Express Mail" mailing label No._EL 989698130 US. Date of Deposit: August 12, 2004. I hereby certify that this paper (and its recited enclosures) or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Commissioner for Patents, MAIL STOP: PATENT EXT., P.O. Box 1450, Alexandria, VA 22313-1450.

	Joseph A. Mahoney
(signature of person mailing paper or fee)	(typed name of person mailing paper or fee)

Commissioner for Patents
MAIL STOP: PATENT EXT.
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Enclosed herewith are the following for the above-captioned application:

1. Original and two (2) copies of a Patent Term Extension Application for U.S. Patent No. 6,489,346;

2. Declaration of David C. Yeomans, Ph.D., in support of PTE (including Exhibits A – H);

3. Two (2) copies of Certificates of Correction previously filed in U.S. Patent No. 6,489,346;

4. Copy of a Terminal Disclaimer filed in U.S. Patent No. 6,489,346;

5. Copy of USPTO Maintenance Fee Report in U.S. Patent No. 6,489,346;

6. Copy of U.S. Patent No. 6,489,346; and

7. Return receipt postcard.

The Commissioner is hereby authorized to charge the filing fees in the amount of $1,220.00 to Deposit Account 13-0019 in addition to any other fees that may be required for this filing.

Respectfully submitted,

Joseph A. Mahoney
Reg. No. 38,956

Date: August 13, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Phillips, J.O.	)	ATTORNEY DOCKET:	01723326
PATENT NO.:	6,489,346	)	GROUP ART UNIT:	1625
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[signature]	Joseph A. Mahoney
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Alexandria, VA 22313-1450

Sir:

APPLICATION FOR PATENT TERM EXTENSION

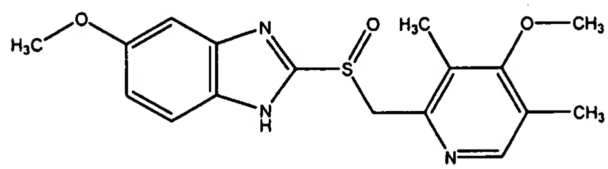
Pursuant to the provisions of 35 U.S.C. § 156, The Curators of the University of Missouri (hereinafter "Missouri") hereby requests an extension of the term of U.S. Patent No. 6,489,346 (hereinafter the '346 patent) of 433 days, from July 15, 2016 to September 22, 2017. Missouri is the owner of record of the '346 patent and Santarus, Inc. (hereinafter "Santarus") is the exclusive licensee of the '346 patent pursuant to an agreement executed on January 26, 2001. Information used in preparing this application, including the response to 37 C.F.R. § 1.740(a)(11), was obtained, at least in part, from Santarus.

Applicant hereby provides the following information as required by 37 C.F.R. § 1.740(a):

Section 1: Complete identification of the approved product.

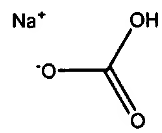
The approved product, Zegerid™ Powder for Oral Suspension, comprises omeprazole (20 mg strength) as an active ingredient, sodium bicarbonate (1680 mg) which acts to protect the omeprazole from acid degradation in gastrointestinal fluids, and several inactive ingredients including sucrose, sucralose, xanthan gum, xylitol, and flavorings.

Omeprazole has the following chemical formula:



and its chemical name is 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1*H*-benzimidazole. The empirical formula for omeprazole is $C_{17}H_{19}N_3O_3S$ and its molecular weight is 345.42.

Sodium bicarbonate has the following chemical formula:



The empirical formula for sodium bicarbonate is $CHNaO_3$ and its molecular weight is 84.01. A copy of the FDA approval letter in regards to Zegerid™ is attached herewith as **Attachment 1**.

According to the Manual of Patent Examining Procedure ("M.P.E.P.")., *Eighth Edition*, Revision 2 (§ 2752, page 2700-32), "an approved product having two active ingredients, which are ***not shown to have a synergistic effect or have pharmacological interaction***, will not be considered to have a single active ingredient made of the two active ingredients." (emphasis added). Therefore, according to the M.P.E.P., an approved drug product having two or more active ingredients, which are shown to have a synergistic effect or a pharmacological interaction should be considered to have a single active ingredient made of the two active ingredients. The term "active ingredient" is defined in the M.P.E.P. (§ 2752, page 2700-31) to be "the ingredient in the drug product that becomes therapeutically active when administered."

Zegerid™ Powder for Oral Suspension is an immediate-release formulation that contains omeprazole (an acid labile proton pump inhibitor) and sodium bicarbonate which is present, *inter alia*, to raise the pH of the gastrointestinal fluid thereby protecting omeprazole from acid

degradation in the gastrointestinal tract and allowing for absorption of omeprazole in the stomach.

As supported by the Declaration of David C. Yeomans, Ph.D., of Stanford University, submitted herewith and incorporated by reference herein, Applicant has shown both a pharmacological interaction and a synergistic interaction between omeprazole and sodium bicarbonate. *See, e.g.*, Declaration of Dr. David Yeomans at ¶¶ 7-9.

Although the FDA labeling does not indicate that sodium bicarbonate is an active ingredient, this is not dispositive for purposes of patent term extension. Congress has granted to the United States Patent and Trademark Office ("PTO"), not the FDA, the authority to determine whether a patent is eligible for patent term extension under 35 U.S.C. § 156. Therefore, in determining the "active ingredient" of Zegerid™ for purposes of patent term extension, the PTO should not look to what was ultimately listed as the active ingredient on the FDA label, but rather, the PTO should independently determine what constitutes the "active ingredient" for purposes of 35 U.S.C. § 156.

"The Manual of Patent Examining Procedure (MPEP) contains details of the practices and procedures whereby the PTO implements its statutory mission." *Exxon Corp. v. Phillips Petroleum Co.*, 265 F.3d 1249, 1251 (Fed. Cir. 2001). Again, the M.P.E.P. defines "active ingredient" to be "the ingredient in the drug product that becomes therapeutically active when administered." (§ 2752, page 2700-31). Applicant hereby submits that it is the *combination* of omeprazole and sodium bicarbonate that becomes therapeutically active for the approved uses of Zegerid™. *See, e.g.*, Declaration of Dr. David Yeomans at Figure 1. In other words, without sodium bicarbonate or another buffering agent as provided by the '346 patent, the omeprazole would degrade in the gastrointestinal fluid, thereby significantly decreasing or eliminating altogether its therapeutic effectiveness for the approved uses. *See, e.g.*, *Id.* at ¶¶ 38-39. Therefore, Applicant submits that the PTO should consider both omeprazole and sodium bicarbonate to be active ingredients for purposes of patent term extension and therefore that Zegerid™ has a single active ingredient made up of these two ingredients.

Section 2: Complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355), section 505(b)(2).

Section 3: Identification of the date on which the product received permission for commercial marketing.

Zegerid™ received permission for commercial marketing or use under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on June 15, 2004.

Section 4: Identification of each active ingredient.

As discussed above and in the Declaration of David C.Yeomans, Ph.D., attached herewith, omeprazole and sodium bicarbonate act together to produce the pharmacological interaction of Zegerid™. For example, without sodium bicarbonate or another buffering agent as provided by the '346 patent, the omeprazole present in Zegerid™ would degrade in gastrointestinal fluid and would not become therapeutically active. As such, the new active ingredient, for purposes of patent term extension under 35 U.S.C. § 156, is a combination of omeprazole/sodium bicarbonate, which has not been previously approved for commercial marketing or use.

It is Missouri's understanding that **enteric coated granules** of omeprazole were first approved for commercial marketing or use under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on September 14, 1989 (*i.e.* Prilosec®). It is also pointed out that sodium bicarbonate has been approved as an active ingredient in prescription products including, for example, Baros (approved August 7, 1985) and BSS Plus (approved October 28, 1981).

As detailed in the '346 patent and herein, the omeprazole/sodium bicarbonate combination under consideration is markedly different from both the enteric coated granules of Prilosec® and sodium bicarbonate as single agents.

Section 5: Timeframe for submission.

This application is being timely submitted within the sixty-day period provided by 35 U.S.C. § 156(d)(1) since approval was granted on June 15, 2004 and the sixty-day period will expire on Saturday, August 14, 2004.

Section 6 and 7: Compete identification of the patent and copy of the patent.

The patent for which an extension is sought is:

U.S. Patent No.:	6,489,346
Issued:	December 3, 2003
Inventor:	Jeffrey O. Phillips
Filed:	January 11, 2000
Expires:	July 16, 2016

A copy of U.S. Patent No. 6,489, 346 is enclosed herewith as **Attachment 2**.

Section 8: Copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

Enclosed as **Attachment 3** is a schedule of maintenance fee payments (none have yet come due), as **Attachment 4** a copy of a Terminal Disclaimer filed during prosecution of U.S. Patent No. 6,489,346, and as **Attachment 5** two certificates of correction filed regarding U.S. Patent No. 6,489,346.

Section 9: Statement that the patent claims the approved product and a method of using the approved product.

U.S. Patent No. 6,489,346 claims the approved product and methods of using the approved product. The applicable claims of the '346 patent are claims 24, 26, 31-35, 37, 50 – 53, 55 – 60, 65 – 66, 68, 80 – 86, 90 – 94, and 117 – 118. Below, the applicable claims are provided (single space) followed by a brief description explaining how the claim in question embraces the approved product.

Claims

Claim 24. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject a solid pharmaceutical composition in a dosage

form that is not enteric-coated; wherein the composition comprises active ingredients consisting essentially of:

(a) a therapeutically effective amount of approximately 5 mg to approximately 300 mg of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent in an amount of approximately 1.0 mEq to approximately 150 mEq selected from the group consisting of a bicarbonate salt of a group IA metal, a calcium salt, and a magnesium salt, wherein the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.

Zegerid™ powder for oral suspension is a non-enteric coated solid dosage form (powder) that comprises 20 mg of powder omeprazole and 20 mEq of buffering agent (sodium bicarbonate), which is a bicarbonate salt of a Group IA metal. The buffering agent is present in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect. Therefore, claim 24 reads on the approved product.

Claim 26. The method of claim 24, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg.

The sodium bicarbonate is present in an amount of 1680 mg. Therefore, claim 26 reads on the approved product.

Claim 31. The method of claim 24, wherein the buffering agent is in an amount of at least 10 mEq.

The sodium bicarbonate is present in an amount of 20 mEq. Therefore, claim 31 reads on the approved product.

Claim 32. The method of claim 24, wherein the buffering agent is in an amount from about 10 mEq to about 70 mEq.

The sodium bicarbonate is present in an amount of 20 mEq. Therefore, claim 32 reads on the approved product.

Claim 33. The method of claim 24, wherein the buffering agent is in an amount from about 20 mEq to about 40 mEq.

The sodium bicarbonate is present in an amount of 20 mEq. Therefore, claim 33 reads on the approved product.

Claim 34. The method of claim 24, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 34 reads on the approved product.

Claim 35. The method of claim 24, wherein the proton pump inhibitor is omeprazole.

The proton pump inhibitor is omeprazole. Therefore, claim 35 reads on the approved product.

Claim 37. The method of claim 35, wherein the omeprazole is present in an amount of about 20 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 37 reads on the approved product.

Claim 50. The method of claim 24, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

The composition is in a powder dosage form. Therefore, claim 50 reads on the approved product.

Claim 51. The method of claim 24, wherein the subject is a human.

Zegerid™ powder for oral suspension is approved for the treatment of humans. Therefore, claim 51 reads on the approved product.

Claim 52. The method of claim 24, wherein the dosage form further comprises a flavoring agent.

Zegerid™ powder for oral suspension comprises peach and peppermint flavors. Therefore, claim 52 reads on the approved product.

Claim 53. The method of claim 52, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

Zegerid™ powder for oral suspension comprises peppermint flavor. Therefore, claim 53 reads on the approved product.

Claim 55. The method of claim 24, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

Zegerid™ powder for oral suspension is indicated for short-term treatment of active duodenal ulcers, treatment of heartburn and other symptoms associated with GERD, short-term treatment of erosive esophagitis, and to maintain healing of erosive esophagitis. Therefore, claim 55 reads on the approved product.

Claim 56. The method of claim 24, wherein the dosage form is administered once or twice a day.

The recommended dose of Zegerid™ powder for oral suspension is 20 mg once daily. Therefore, claim 56 reads on the approved product.

Claim 57. A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent selected from the group consisting of sodium bicarbonate, and calcium carbonate, in an amount more than about 40 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

Zegerid™ powder for oral suspension is a non-enteric coated solid dosage form (powder) that comprises 20 mg of non-enteric coated omeprazole (a therapeutically effective amount) and 1680 mg of sodium bicarbonate. The buffering agent is present in an amount of 84 times the amount of the omeprazole on a weight to weight basis. Therefore, claim 57 reads on the approved product.

Claim 58. The composition as recited in claim 57, wherein the buffering agent is sodium bicarbonate.

The buffering agent is sodium bicarbonate. Therefore, claim 58 reads on the approved product.

Claim 59. The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount from about 400 mg to about 4000 mg.

The sodium bicarbonate is present in an amount of 1680 mg. Therefore, claim 59 reads on the approved product.

Claim 60. The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

The sodium bicarbonate is present in an amount of 1680 mg. Therefore, claim 60 reads on the approved product.

Claim 65. The composition as recited in claim 57, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 65 reads on the approved product.

Claim 66. The composition as recited in claim 57, wherein the proton pump inhibitor is omeprazole.

The proton pump inhibitor is omeprazole. Therefore, claim 66 reads on the approved product.

Claim 68. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 20 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 68 reads on the approved product.

Claim 80. The composition as recited in claim 57, wherein the proton pump inhibitor is micronized.

The omeprazole is present in micronized form. Therefore, claim 80 reads on the approved product.

Claim 81. The composition as recited in claim 57, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

Zegerid™ powder for oral suspension is in the form of a powder. Therefore, claim 81 reads on the approved product.

Claim 82. The composition as recited in claim 57, further comprising a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

Zegerid™ powder for oral suspension comprises either peppermint or peach flavoring agent. Therefore, claim 82 reads on the approved product.

Claim 83. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 50 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 83 reads on the approved product.

Claim 84. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 60 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 84 reads on the approved product.

Claim 85. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 70 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 85 reads on the approved product.

Claim 86. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 80 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 86 reads on the approved product.

Claim 90. A method of producing a liquid pharmaceutical composition comprising: combining the dosage form of claim 57 with an aqueous medium.

Prior to administering Zegerid™ powder for oral suspension, the powder is to be combined with 2 tablespoons of water. Therefore, claim 90 reads on the approved product.

Claim 91. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form as recited in claim 57 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

Zegerid™ powder for oral suspension is indicated for treatment of acid-caused gastrointestinal disorders and is to be administered to orally. Therefore, claim 91 reads on the approved product.

Claim 92. The method as recited in claim 91, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

Zegerid™ powder for oral suspension is indicated for short-term treatment of active duodenal ulcers, treatment of heartburn and other symptoms associated with GERD, short-term treatment of erosive esophagitis, and to maintain healing of erosive esophagitis. Therefore, claim 92 reads on the approved product.

Claim 93. The method as recited in claim 91, wherein the composition is administered once or twice a day.

The recommended dose of Zegerid™ powder for oral suspension is 20 mg once daily. Therefore, claim 93 reads on the approved product.

Claim 94. A method for administering a liquid pharmaceutical composition to a subject, comprising: combining the pharmaceutical composition as recited in claim 57 with an aqueous medium to form a suspension, and orally administering the suspension to the subject in a single dose without administering an additional buffering agent.

Zegerid™ powder for oral suspension is indicated to be combined with two tablespoons of water prior to administration. No additional buffering agent is required. Therefore, claim 94 reads on the approved product.

Claim 117. The method of claim 24, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

Zegerid™ powder for oral suspension comprises various excipients. Therefore, claim 117 reads on the approved product.

Claim 118. The method of claim 24, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

Zegerid™ powder for oral suspension comprises various excipients. Therefore, claim 118 reads on the approved product.

Section 10: Relevant dates and information pursuant to 35 U.S.C. 156(g) to enable a determination of the applicable regulatory review period.

1. November 10, 1994	Effective date of IND Application No. 46-656.
2. December 3, 2002	Date of Issuance of U.S. Patent No. 6,489,346.
2. August 15, 2003	Submittal date of NDA No. 21-636.
3. June 15, 2004	Date of approval of NDA No. 21-636.

Section 11: Brief description of the activities undertaken during the applicable regulatory review period with respect to the approved product and significant dates applicable to such activities.

Santarus, the marketing applicant, undertook development of this product to establish, by adequate and well-controlled clinical trials, its safety and effectiveness for short-term treatment of active duodenal ulcer, treatment of heartburn and other symptoms associated with GERD, maintenance of healing of erosive esophagitis, and short term treatment of erosive esophagitis.

The following is a chronology of the activities undertaken by Santarus during the applicable regulatory review period:

Regulatory Review Period Activities for IND 46-656

Type of Correspondence.	Date	Contents
Original IND	11/10/94	Submitted clinical study
Annual Report	2/21/96	As per 21 CFR 312.33
Annual Report	1/27/97	Study publication in Crit Care Med 1996:24:1793
Annual Report	3/27/98	As per 21 CFR 312.33
Annual Report	2/12/99	Clinical update on SOS
Annual Report	2/18/00	Submitted study of SOS
Amendment	4/12/00	Submitted information regarding SOS preparation
Amendment	1/31/01	Letter from University of Missouri to FDA indicating transfer of IND to Santarus
Amendment	2/2/01	Letter from Santarus to FDA acknowledging transfer
Letter from FDA	2/8/01	Letter from FDA acknowledging transfer of IND
Phone Contact	2/8/01	Conference with FDA regarding timing for subsequent discussions regarding clinical development program
Amendment	2/26/01	Letter to FDA regarding clinical studies and CMC information
Phone Contact	4/23/01	Phone call from FDA regarding ChocoBase
Phone Contact	4/26/01	Discussion regarding open-label study
Letter from FDA	6/14/01	Letter from FDA regarding the submission of IND Annual update
Annual Report	6/20/01	As per 21 CFR 213.33
New Protocol	7/6/01	Clinical Amendment: New study, OSB-IR-C01; Sensory

Type of Correspondence.	Date	Contents
CMC Amendment		benchmarking and excipient formulation development for OSB-IR CMC Amendment: DMF for API supplier
Letter from FDA	7/17/01	Letter from FDA denying request for a waiver of the 30 day waiting period
CMC Amendment	7/23/01	Santarus response to reviewer questions
Amendment	8/31/01	Pre-Phase 3 Meeting
Fax from FDA	9/14/01	Fax from FDA confirming the October 30th meeting
Amendment	11/8/01	Submission of Santarus October 30th pre-Phase 3 meeting minutes
Letter from FDA	11/19/01	Letter from FDA acknowledging receipt of change of address
Clinical Amendment	1/15/02	Draft Clinical Protocol and Questions
Letter from FDA	1/15/02	Receipt of FDA version of October 30, 2001 meeting minutes
Clinical Amendment	2/4/02	Additional clinical questions regarding C02 PK/PD study
Phone Contact	2/11/02	Request for teleconference with FDA regarding Phase 3 study questions
Fax from FDA	3/22/02	Fax from FDA documenting the Agency's response to meeting questions
Letter from FDA	3/25/02	Minutes of teleconference with FDA regarding questions about the C02 & C03 trials
Clinical Amendment	3/26/02	Sponsor response to issues from FDA March 25th 2002 teleconference
CMC Amendment	4/4/02	CMC update in support of Phase 3 study
New Protocol	4/5/02	New protocol: OSB-IR-C02; new PI
Change in Protocol	4/11/02	Protocol Amendment 1 - OSB-IR-C03: Transfer of sponsor responsibilities for C03 study
Pediatric Study	4/18/02	Proposed Pediatric Study Request: study summary for pediatric study OSB-IR-C04
New Investigator	5/1/02	New investigator for protocol OSB-IR-C02
CMC Amendment	5/10/02	Analytical test results and DMF authorization letter

Type of Correspondence.	Date	Contents
New Investigators	5/23/02	New Principal Investigators (PIs) for OSB-IR-C03
Letter from FDA	5/28/02	Letter from FDA requesting responses to four CMC questions
Annual Report	5/31/02	IND Annual Report
Updated IB	6/4/02	Updated IB
New Protocol	6/4/02	New protocol - OSB-IR-C05
Change in Protocol	6/14/02	Protocol Amendment 1 - OSB-IR-C02
New Investigators	7/3/02	New PIs for OSB-IR-C03
Change in Protocol Clinical Amendment	7/12/02	OSB-IR-C02 - Protocol Amendment 2 and Statistical Analysis Plan; Administrative Analysis Plan for Phase 3 Study OSB IR-C03
Meeting Request	7/24/02	Meeting request to discuss 505(b)(2) NDA based on PK/PD data
Letter from FDA	7/31/02	FDA issued a letter to Santarus requesting Santarus review the SAN-05 C03 protocol to determine whether it should be registered in the Clinical Trial Data Bank
New Investigators	8/1/02	New PIs for OSB-IR-C03
Letter from FDA	08/13/02	FDA issued a letter giving comments & recommendations referring to the IND and 3/26/02 and 4/18/02 Amendments
CMC Amendment	8/19/02	Response to June 2, 2002 FDA CMC questions
New Investigators	9/09/02	New PIs for OSB-IR-C03
CMC Amendment	09/13/02	Amendment for OSB-IR-C06, Phase 1
New Protocol - C06	09/18/02	New Protocol OSB-IR-C06
Letter from FDA	09/23/02	Receipt of FDA version of March 25, 2002 meeting minutes
Letter from FDA	10/10/02	Letter from the FDA: response to the Proposed Pediatric Study Request; study summary for pediatric study OSB-IR C04
Feedback	10/11/02	Pre-NDA Request for Feedback

Type of Correspondence.	Date	Contents
Request		
Feedback Request	11/15/02	Letter to the FDA: requesting a feedback on proposed trademarks for OSB-IR
New Investigators	12/03/02	New PIs for OSB-IR-C03
Clinical Amendment	12/11/02	Statistical Analysis Plan for Study OSB-IR-CO5 & OSB-IR C06
Letter from FDA	12/31/02	FDA issued a letter to Santarus requesting Santarus review the SAN-05 C06 new protocol to determine whether it should be registered in the Clinical Trial Data Bank
Pre-NDA CMC Meeting Request	01/24/03	Letter to the FDA requesting a CMC Type B meeting in March
Pre-NDA CMC Additional. Data	02/03/03	Letter to FDA giving additional PK/PD data requested at the January 27, 2003 meeting
Fax to FDA	02/04/03	Faxed a copy of the Letter to FDA giving additional PK/PD data sent 02/03/03 to the FDA
New Investigator	02/07/03	New PIs for OSB-IR-C03
Pre-NDA CMC Meeting Background Package	02/17/03	Pre-meeting background package in preparation for the March 20, 2003 pre-NDA CMC meeting regarding OSB-IR
Fee Waiver Request	03/07/03	Request for small business fee waiver
Response to Fee Waiver Request	03/07/03	FDA acknowledgment letter sent in response to the Small Business Waiver Santarus' Request
US SBA Letter: Requirements for Size Determination	03/10/03	US SBA (Small Business Administration): letter explaining the requirements for qualifying a small size business, including Application for Small Business Size Determination Form
Fax from FDA Answers to Pre-NDA CMC Meeting	03/18/03	FDA answers to the Pre-NDA CMC meeting
Santarus answers to US SBA - Size Determination	03/24/03	Santarus letter sent to US SBA re: Requirements for a small size business determination

Type of Correspondence.	Date	Contents
FDA Fax: Feedback on Oct 11, 2002 & Amendment	03/26/03	FDA feedback about the IND submission, Pre NDA clinical feedback
Letter from FDA	03/26/03	FDA feedback about the IND submission, Pre NDA clinical feedback (received 03/28/03.)
Letter from US SBA	03/27/03	Additional information request for the NDA small business fee waiver
Letter to US SBA	03/28/03	Information requested for small business fee waiver sent to US Small Business Administration
Request for Tele-conference with FDA	04/03/03	Request for Teleconference with FDA following the answer from FDA 03/26/03
US SBA Letter Acceptation of Small Business Status	04/07/03	Letter indicating that Santarus was determined to be a small business
Letter from FDA	04/15/03	FDA minutes of the 20 Mar 03 CMC meeting (received by Santarus on 05/02/03).
New Investigators	04/22/03	Protocol Amendment: New investigators and subinvestigators for study OSB-IR-C03.
Letter to HHS	05/09/03	Registration of Drug Establishment and document with Receipt date returned to Santarus by HHS
Background Package	05/13/03	Background Package for June 10, 2003 meeting
Letter from FDA: Labeler code No: 68012	05/15/03	Letter from FDA: Labeler code No: 68012
Amendment to Background Package	05/23/03	Amendment to June 10 Premeeting Background Package
Annual Report	05/30/03	Annual report sent to FDA.
Fax from FDA	06/06/03	FDA answers to questions for June 10 meeting.
FDA Letter: Answers to Questions Meet	06/09/03	FDA letter: answers to questions for June 10 meeting
New	06/26/03	Clinical Amendment: New investigators for study OSB-IR

Type of Correspondence.	Date	Contents
Investigators		C03.
FDA Letter: June 10 Meeting Minutes	07/14/03	Letter from FDA: Official minutes of June 10 meeting
Clinical Amendment	07/22/03	Statistical Analysis Plan for OSB-IR-C03
Request for CMC Information	09/10/03	CMC request for information re: content and format, etc.
Protocol Amendment New Investigator	10/08/03	Clinical amendment: Protocol Amendment 1 for OSB-IR-C07 and new investigator
New Investigator	11/18/03	Clinical amendment: new investigators for OSB-IR-C07.
Statistical Analysis Plan	11/21/03	Clinical Amendment: Statistical Analysis Plan for OSB-IR C07.
Letter from FDA CMC Response	12/02/03	Response to CMC questions asked during 6/10/03 meeting
Letter from FDA OSB-IR-C07 Protocol	12/18/03	Response to the Clinical Trial Protocol OSB-IR-C07 submitted on 10/8/03
Clinical Reports	04/02/04	Clinical Amendment requesting Agency to refer to the NDA 21-636 for the Clinical Trials Reports of C02, C05 and C06
Annual Report	05/25/04	Annual Report including a new Investigator's Brochure

Regulatory Review Period Activities for NDA 21-636

Type of Correspondence.	Date	Contents
Letter to FDA: Original NDA	08/14/03	Original New Drug Application
Letter to FDA: Extra desk copies	08/18/03	3 extra desk copies of Module 1 sent to FDA
Letter to FDA: Paper Review Copies	09/09/03	3 copies of Module 2, 3 copies of Module 5 and 1 copy of Module 3 sent to FDA

Type of Correspondence.	Date	Contents
Letter from FDA	09/29/03	Letter stating the receipt of the application
Patent Certification	10/15/03	Certification letter of the patent notification to interested parties of our NDA filing
Fax from FDA **Filing Review Letter**	10/24/03	Fax from FDA acknowledging the filing review letter
Letter to FDA	11/07/03	Documentation of return receipts of notice of Paragraph IV patent certification, as per 21 CFR 314.52(e)
Letter from FDA	11/14/03	Letter from FDA – Filing Review – Sent 10-24-03
Patent Information 003	12/09/03	Patent information sent to FDA
Safety Update	01/07/04	120-Day Safety Update sent to FDA
Response to FDA Filing Letter	01/15/04	Response to FDA filing review letter
Fax from FDA-CDR	01/20/04	Letter from FDA CDER Electronic Document Room Staff regarding Amendment previously submitted
E-mail to FDA	01/29/04	E-mail to FDA concerning the trade name for OSB-IR 20 mg
Fax from FDA	02/09/04	FDA faxed the letter with Tradename and labeling comments
FDA Letter	02/16/04	FDA letter with Tradename and labeling comments
DP Stability Update	02/18/04	Letter to FDA with the Drug Product Stability and Specification Update
Proposed Labeling	02/24/03	Letter to FDA regarding Proposed Labeling Text sent on a CD
FDA Letter	03/01/04	Information Request Letter regarding the CMC section
FDA Letter	03/01/04	Recommendation for Labeling: organization of the Clinical Pharmacology
Response to Disc Rev Letter	03/02/04	Letter and CD-ROM sent to Doc Control Room with Santarus response to February 9, 2004 Discipline Review Letter
Stability Update	03/11/04	Letter to FDA: Stability update

Type of Correspondence.	Date	Contents
FDA Fax	03/18/04	Fax from FDA: CMC Discipline Review Letter
Final Labeling	03/22/04	Letter to FDA: Final Labeling
FDA Letter	03/22/04	Letter from FDA: CMC Discipline Review Letter
Patent Information	03/30/04	Letter to FDA: new patent information, Form 3542a
CMC & Labeling	04/05/04	Letter to FDA: Complete Response to March 16, 2004 Discipline Review Letter, included CMC and Labeling sections
Fax to FDA	04/07/04	Fax sent to FDA: Complete Response to March 16, 2004 Discipline Review Letter, included only the CMC section
Revised PI	04/09/04	Letter to FDA: Revised Prescribing Information
E-mail to FDA Labels	04/14/04	E-mail to FDA with packet and carton labels
Follow-up to 15 Apr 04 Teleconference	04/19/04	Letter sent to FDA with the Follow-up to 15 April 04 CMC Teleconference
Proposed Revisions to Labeling	04/20/04	Letter to FDA with the Proposed Revisions to Labeling.
Fax from FDA Labeling Comments	04/22/04	Fax from FDA: Comments about the Labeling for the Teleconference that will be held with FDA on April 26, 2004
E-mail from FDA	04/26/04	Labeling: Word version of FDA revision of Prescribing Information after teleconference meeting on April 26, 2004
Prescribing Info	04/27/04	Letter to FDA: Prescribing Information – New draft incorporating comments made at April 26, 2004 Labeling Teleconference
Revised Labeling	05/13/04	Revised Labeling: revised packets and cartons labeling (color labels)
E-mail from FDA	05/14/04	Labeling: Word version of FDA revision of Prescribing Information response to prescribing information sent on 4/27/04
Revised Labeling	05/18/04	Revised Labeling: prescribing information in pdf and Word format, packets and labels in Word format

Type of Correspondence.	Date	Contents
Letter from FDA	05/20/04	Response to Amendment, dated March 2, 2004, Trade Name and labeling
E-mail form FDA	05/25/04	DMETS comments to sponsor regarding the Trade Name
Briefing Package	05/28/04	for June 7, 2004 meeting with FDA regarding Trade Name
E-mail from FDA	06/02/04	Requested a copy of amendment to paragraph IV certification
Fax from FDA	06/04/04	Responses to questions for the June 7, 2004 meeting
Fax from FDA	06/07/04	CDER Electronic Document Room Staff: request for resubmission of amendment submitted 5/28
Background Info for June 7, 2004 Meeting	06/07/04	Background information given to FDA including: PI dated May 18, 2004, PI dated June 04, 2004, Labels and PI of eight other drugs
June 7, 2004 Agenda	06/07/04	June 07, 2004 meeting FDA agenda
E-mail from FDA	06/10/04	FDA Final Label
E-mail to FDA	06/11/04	Final Label (Package Insert) for "Rapinex" with edits
E-mail to FDA	06/14/04	Carton and Trade Labels without the Trade Name "Rapinex"
FDA Fax	06/15/04	Approval Letter and Final Printed Labeling (FPL)
FDA Approval Letter	06/15/04	Approval Letter and Final Printed Labeling (FPL)

<u>Section 12: Patent eligibility and the length of extension claimed</u>.

U.S. Patent No. 6,489,346 is eligible for extension for 433 days since:

(a) It claims (1) the approved human drug product Zegerid™, and (2) the use of the approved human drug product;

(b) The term of said patent has never previously been extended;

(c) This application is submitted by the owner of record of the patent, The Curators of the University of Missouri;

(d) The product has been subject to regulatory review prior to the commercial marketing or use under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act;

(e) The product received permission for commercial marketing or use on June 15, 2004, and the application has been submitted within 60 days from that date;

(f) The permission for commercial marketing or use of the product is believed to be the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act under which the regulatory review period occurred;

(g) The term of the patent has not expired prior to this date of application; and

(h) No other patent term has been extended for the same regulatory review period for this product;

(i) As shown in the Declaration of David C. Yeomans, Ph.D., attached herewith, both a synergy and a pharmacological interaction exists between omeprazole and sodium bicarbonate. As discussed above, according to the M.P.E.P., an approved drug product having two or more active ingredients which are shown to have a synergistic effect or a pharmacological interaction should be considered to have a single active ingredient made of the two active ingredients. The term "active ingredient" is defined in the M.P.E.P. (§ 2752, page 2700-31) to be "the ingredient in the drug product that becomes therapeutically active when administered." Applicant submits that it is the combination of omeprazole and sodium bicarbonate that becomes therapeutically active for the approved uses of Zegerid™.

The original expiration date of the patent from which the patent term extension will run is July 16, 2016 (as limited by a terminal disclaimer based on U.S. Patent No. 5,840,737).

The length of extension claimed is **433** days and was calculated as follows:

A regulatory review period (per 37 C.F.R. § 1.775(c)) of 3518 days was calculated as the sum of:

(1) the number of days from the filing of IND No. 46-656, November 10, 1994, to the filing date of the NDA, August 15, 2003, or 3214 days; and

(2) the number of days from the filing date of the NDA, August 15 2003, to the date of approval of the NDA, June 15, 2004, or 304 days.

The term of extension is generally determined under 37 C.F.R. § 1.775(d) by subtracting from the number of days determined to be the regulatory review period, the following:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued, which in this case is 2943 days (from November 10, 1994 – December 3, 2002);

(ii) The number of days in the regulatory review period in which it is determined that the marketing applicant did not act with diligence (zero); and

(iii) One-half of the number of days remaining in the period defined by 37 C.F.R. § 1.775(c)(1) after that period is reduced in accordance with 37 C.F.R. §§ 1.775(d)(1)(i) and (ii).

Importantly, the date to which the patent may be extended cannot exceed the earlier of 14 years from the date of approval of the NDA, or for patents issued after September 24, 1984, five years from the original expiration date of the patent.

Assuming there is a determination that there are no periods in which the marketing applicant failed to act with due diligence, the calculation under 37 C.F.R. §§ 1.775(d)(1) is as follows:

3507	The regulatory review period is calculated as the period starting on November 10, 1994 [day 1] up to and including June 15, 2004 [day 3507];
- 2946	The period starting on November 10, 1994 [day 1] up to and including December 3, 2002 [day 2946];
- 0	No lack of due diligence is assumed;
- ½ (3202-2946)	0.5 x (the period beginning on November 10, 1994 [day 1] up to and including August 15, 2003 [day 3202] – the period beginning on November 10, 1994 up to and including December 3, 2002).
433	

This number of days does not exceed five years and the record clearly indicates that Applicants were diligent. Therefore, Missouri submits that the term of U.S. Patent No. 6,489,346 should be extended for 433 days, from July 16, 2016 to September 22, 2017.

Section 13: Duty of Disclosure.

The applicant hereby acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Section 14: Fees.

The prescribed fee of $1,120.00 for receiving and acting upon the application for extension should be debited from Deposit Account No. 13-0019. If additional fees are required, authorization is made to charge such fees to Deposit Account No. 13-0019.

Section 15: Correspondence Address.

Inquiries and correspondence should be addressed to:

Joseph A. Mahoney, Esq.
Reg. No. 38,956
Mayer, Brown, Rowe & Maw LLP
P.O. Box 2828
Chicago, IL 60690
(312) 701-8979

Section 16: Copies.

The original and two (2) duplicate copies of this application are being submitted pursuant to 37 C.F.R. § 1.740(b) and it is hereby certified that the copies are identical to the original.

Section 17: Declaration.

The undersigned:

1. Is a patent attorney authorized to practice before the Patent and Trademark Office who has general authority from the owner of record of U.S. Patent No. 6,489,346 to act on behalf of the owner in patent matters;
2. Has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.740;
3. Believes U.S. Patent No. 6,489,346 is subject to extension pursuant to 37 C.F.R. § 1.710 and 35 U.S.C. § 156;
4. Believes an extension for 433 days, the length claimed, is justified under 35 U.S.C. § 156 and the applicable regulations; and
5. Believes the patent for which the extension is being sought meets the conditions for extension of the term of the patent as set forth in 37 C.F.R. § 1.720.

Any questions concerning this application may be directed to the below noted attorney.

Respectfully submitted,

By: Mayer, Brown, Rowe & Maw LLP

By:

Joseph A. Mahoney, Reg. No. 38,956

CUSTOMER NUMBER 26565
MAYER, BROWN, ROWE & MAW LLP
P.O. Box 2828
Chicago, IL 60690-2828
Telephone: (312) 701-8979
Facsimile: (312) 706-9000

Enclosures:

Attachment 1: FDA Approval Letter.

Attachment 2: U.S. Patent No. 6,489,346.

Attachment 3: Maintenance Fee schedule in respect of U.S. Patent No. 6,489,346.

Attachment 4: Terminal Disclaimer filed in respect of U.S. Patent No. 6,489,346.

Attachment 5: Two Certificates of Correction filed in respect of U.S. Patent No. 6,489,346.

Attachment 6: Declaration of Dr. David C. Yeomans (including Exhibits A – H).

tab 1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 15, 2004

To: Christine Simmons, Pharm.D.	**From:** Paul E. Levine, Jr., P.D., J.D.
Company: Santarus, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: 858-314-5701	**Fax number:** (301) 827-1305
Phone number:	**Phone number:** 301-443-8347

Subject: Certification Form

Total no. of pages including cover: 17

Comments:

Document to be mailed: ☐ YES ☑ NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-636

Santarus, Inc.
Attention: Christine Simmons, Pharm.D.
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

Please refer to your new drug application (NDA) dated August 14, 2003, received August 15, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole) Powder for Oral Suspension, 20 mg.

We acknowledge receipt of your submissions dated December 9, 2003; January 7 and 15, February 9, 13, 19, and 26, March 2, 11, 16, 22, and 30, April 5 9, 15, 19, 20, and 26, May 11, 13, 18, 19, and 28, June 2, 8, and June 14, 2004.

This new drug application provides for the use of omeprazole powder for suspension 20 for short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; and maintenance of healing of erosive esophagitis.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use of Zegerid (omeprazole) Powder for Oral Suspension, 20 mg, as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted June 14, 2004). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the products misbranded and an unapproved new drug.

The electronic labeling rule published December 11, 2003 (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e. package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 2 to 16 years until July 15, 2007.

Your deferred pediatric studies for GERD (symptomatic GERD and Erosive Esophagitis) required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 2 to 11 years.

Protocol submission by:	December 15, 2004 (6 mos. post-approval)
Study start:	July 15, 2005 (1 year post-approval)
Final report submission:	July 15, 2007 (3 years post approval)

2) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 12 to 16 years.

Protocol submission by:	December 15, 2004 (6 mos. post-approval)
Study start:	July 15, 2005 (1 year post-approval)
Final report submission:	July 15, 2007 (3 years post approval)

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

(See appended electronic signature page)

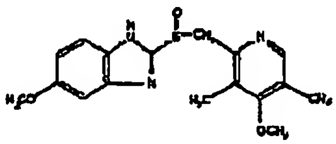
Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Labeling

Zegerid (omeprazole)
Powder for Oral Suspension

DESCRIPTION

The active ingredient in Zegerid (omeprazole) powder for oral suspension, is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1*H*-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Zegerid Powder for Oral Suspension is supplied in unit dose packets as an immediate release formulation to be constituted with water for oral administration. Each packet contains 20 mg of omeprazole and the following excipients: sodium bicarbonate, sucrose, sucralose, xanthan gum, xylitol, and flavorings.

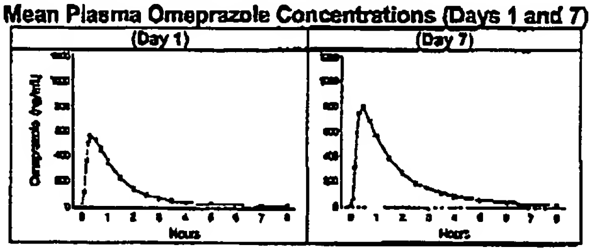
CLINICAL PHARMACOLOGY

Omeprazole is acid labile and thus rapidly degraded by gastric acid. Zegerid Powder for Oral Suspension is an immediate-release formulation that contains sodium bicarbonate to protect omeprazole from acid degradation.

Pharmacokinetics:
Absorption

When Zegerid is administered on an empty stomach 1 hour prior to a meal, absorption of omeprazole is rapid, with mean peak plasma levels of omeprazole occurring at around 30 minutes (range 10 to 90 minutes) after a single dose or repeated once-daily administration (see figures below).

Mean Plasma Omeprazole Concentrations (Days 1 and 7)



The AUC(0-inf)(ng*hr/mL) was 1446 after 7 days of 20 mg daily doses and the Tmax was approximately 30 minutes.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from Zegerid are approximately proportional from 20 to 40 mg doses, but a greater than linear mean AUC (three-fold increase) is

observed when doubling the dose to 40 mg. The bioavailability of omeprazole from Zegerid Powder for Oral Suspension increases upon repeated administration of Zegerid.

Pharmacokinetic Parameters of Zegerid Following Oral 20 mg Once-Daily Dosing for 1 and 7 Days

Parameter	Day 1
AUC(0-inf) (ng*hr/mL)	825
Coefficient of variation	72%
Cmax (ng/mL)	672
Coefficient of variation	44%
Tmax (min)	29.8
T½ (hr)	0.86

Values represent arithmetic means.

Parameter	Day 7
AUC(0-inf) (ng*hr/mL)	1446
Coefficient of variation	61%
Cmax (ng/mL)	902
Coefficient of variation	40%
Tmax (min)	28.3
T½ (hr)	1.08

Values represent arithmetic means.

When Zegerid is administered 1 hour after a meal, Cmax and AUC are reduced by 63% and 24%, respectively, relative to administration prior to a meal.

Distribution
Omeprazole is bound to plasma proteins. Protein binding is approximately 95%.

Metabolism
Absolute bioavailability (compared to intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to pre-systemic metabolism.

Excretion
In healthy subjects, the mean plasma half-life is 1 hour (range 0.4 to 3.2 hours), and the total body clearance is 500-600 mL/min.

Following single dose oral administration of omeprazole, little if any unchanged drug is excreted in urine. The majority of the dose (about 77%) is eliminated in urine as at least six metabolites. Two metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

Special Populations
Geriatric
The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly subjects, versus 58% in young subjects given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young subjects) and its plasma half-life averaged one hour, similar to that of young healthy subjects.

Pediatric
The pharmacokinetics of Zegerid have not been studied in patients < 18 years of age.

Gender
There are no known differences in the absorption or excretion of omeprazole between males and females.

Hepatic insufficiency
In patients with chronic hepatic disease, the bioavailability of omeprazole increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the mean plasma half-life of the drug increased to nearly 3 hours compared to the mean half-life of 1 hour in healthy subjects. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects.

Renal Insufficiency
In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

Asians
In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

Drug-Drug Interactions
When omeprazole 40 mg once daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects, the steady-state plasma concentrations of omeprazole were increased by the concomitant administration of clarithromycin (Cmax, AUC $_{0-24}$ and T1/2 increased 30%, 89%, and 34%, respectively).

Pharmacodynamics

Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

Results from a study of the antisecretory effect of repeated once-daily dosing of 20 mg of Zegerid in healthy subjects (n = 28) is shown below.

Effect of Zegerid 20 mg on Intragastric pH on Day 7 (19)

Parameter	
% Decrease from Baseline for Integrated Intragastric Acidity (mmol-hr/L)	82%/(24%)*
% Time Gastric pH > 4 (hours)	51% (12.2 h) /(43%)*
Median pH	4.2/(37%)*

Values represent medians. All parameters were measured over a 24-hour period.
* Coefficient of variation

The antisecretory effect thus lasts far longer than would be expected from the very short plasma half-life (1 hour) apparently due to irreversible binding to the parietal H+/K+ ATPase enzyme. Repeated single daily oral doses of Zegerid20 mg have produced nearly 100% inhibition of 24-hour integrated intragastric acidity in some subjects.

Enterochromaffin-like (ECL) Cell Effects

In 24 month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists. Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL PHARMACOLOGY, Pathological Hypersecretory Conditions.)

However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of omeprazole 40 mg b.i.d. for 12 months followed by 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also CLINICAL PHARMACOLOGY, Enterochromaffin-like (ECL) Cell Effects).

Clinical Studies

Duodenal Ulcer Disease
Active Duodenal Ulcer - In a multicenter, double-blind, placebo controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with omeprazole 20 mg once a day than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer % of Patients Healed		
	Omeprazole 20 mg a.m. (n = 99)	Placebo a.m. (n = 48)
Week 2	*41	13
Week 4	*75	27
*($p \leq 0.01$)		

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with omeprazole 20 mg once a day than with ranitidine 150 mg b.i.d. ($p < 0.01$).

Treatment of Active Duodenal Ulcer % of Patients Healed		
	Omeprazole 20 mg a.m. (n = 145)	Ranitidine 150 mg b.i.d. (n = 148)
Week 2	42	34
Week 4	*82	63
*($p < 0.01$)		

Healing occurred significantly faster in patients treated with omeprazole than in those treated with ranitidine 150 mg b.i.d. ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of omeprazole were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of omeprazole were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of omeprazole, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer % of Patients Healed			
	Omeprazole		Ranitidine
	20 mg (n = 34)	40 mg (n = 36)	150 mg b.i.d. (n = 35)
Week 2	*83	*83	53
Week 4	*97	*100	82
Week 8	100	100	94
*($p \leq 0.01$)			

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown below:

% Successful Symptomatic Outcome*			
	Omeprazole 20 mg a.m.	Omeprazole 10 mg a.m.	Placebo a.m.
All patients	46*,† ($n = 205$)	31† ($n = 199$)	13 ($n = 105$)
Patients with confirmed GERD	56*,† ($n = 115$	36† ($n = 109$	14 ($n = 59$)
*Defined as complete resolution of heartburn			
*($p < 0.005$) versus 10 mg			
†($p < 0.005$) versus placebo			

Erosive Esophagitis

In a US multicenter double-blind placebo controlled study of 20 mg or 40 mg of omeprazole in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

Week	20 mg Omeprazole ($n = 83$)	40 mg Omeprazole ($n = 87$)	Placebo ($n = 43$)
4	39*	45*	7
8	74*	75*	14
*($p < 0.01$) Omeprazole versus placebo.			

In this study, the 40 mg dose was not superior to the 20 mg dose of omeprazole in the percentage healing rate. Other controlled clinical trials have also shown that omeprazole is effective in severe GERD. In comparisons with histamine H2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, omeprazole in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with omeprazole than in those taking placebo or histamine H2-receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Long Term Maintenance Treatment of Erosive Esophagitis

In a U.S. double-blind, randomized, multicenter, placebo controlled study, two dose regimens of omeprazole were studied in patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown below.

Life Table Analysis			
	Omeprazole 20 mg q.d. ($n = 138$)	Omeprazole 20 mg 3 days per week ($n = 137$)	Placebo ($n = 131$)
Percent in endoscopic remission at 6 months	*70	34	11
*($p < 0.01$) Omeprazole 20 mg q.d. versus Omeprazole 20 mg 3 consecutive days per week or placebo.			

In an International multicenter double-blind study, omeprazole 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

Life Table Analysis			
	Omeprazole 20 mg q.d. (n = 131)	Omeprazole 10 mg q.d. (n = 133)	Ranitidine 150 mg b.i.d. (n = 128)
Percent in endoscopic remission at 12 months	*77	‡58	46
*(p = 0.01) Omeprazole 20 mg q.d. versus Omeprazole 10 mg q.d. or Ranitidine.			
‡(p = 0.03) Omeprazole 10 mg q.d. versus Ranitidine.			

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of omeprazole was effective, while 10 mg did not demonstrate effectiveness.

INDICATIONS AND USAGE

Duodenal Ulcer

Zegerid is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

Zegerid is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

Zegerid is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

(See CLINICAL PHARMACOLOGY, Clinical Studies.)

The efficacy of Zegerid used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (e.g. heartburn), additional 4-8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis

Zegerid Powder for Oral Suspension is indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

CONTRAINDICATIONS

Zegerid is contraindicated in patients with known hypersensitivity to any components of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Zegerid contains 460 mg sodium per dose in the form of sodium bicarbonate. This should be taken into consideration for patients on a sodium-restricted diet.

Zegerid contains 1680 mg (20 mEq) of sodium bicarbonate. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, and respiratory alkalosis. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

Information for Patients
Zegerid is supplied as a powder for oral suspension. It should be taken on an empty stomach at least 1 hour prior to a meal.

Zegerid is available as 20 mg single-dose packets. Directions for use: Empty packet contents into a small cup containing 2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

Drug Interactions
Other

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in healthy subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with Zegerid.

Because of its profound and long-lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of omeprazole.

Co-administration of omeprazole and clarithromycin have resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin (see also **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg per day, based on body surface area) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.7 times the human dose of 20 mg per day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose of 20 mg/day, based on body surface area). No

astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 57 times the human dose of 20 mg per day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an in vivo bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138.0 mg/kg/day (about 56 times the human dose of 20 mg per day, based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. In utero exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at omeprazole doses up to 138 mg/kg/day (about 56 times the human dose of 20 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 56 times the human dose of 20 mg per day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.6 to 56 times the human dose of 20 mg per day, based on body surface area) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose of 20 mg per day, based on body surface area).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase. There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration will correspond to 0.004 mg of omeprazole in 200 mL of milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (about 5.6 to 56 times the human dose of 20 mg per day, based on body surface area) resulted in decreased weight gain in pups. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate should be used with caution in nursing mothers.

Pediatric Use

There are no adequate and well-controlled studies in pediatric patients with Zegerid.

Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies with omeprazole have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young subjects). The plasma half-life averaged one hour, about the same as that in nonelderly, healthy subjects taking Zegerid. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Omeprazole was generally well tolerated during domestic and international clinical trials in 3096 patients.

In the US clinical trial population of 465 patients, the following adverse experiences were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)

Rash	1.5 (1.1)	0.0	0.0
Constipation	1.2 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole.

Incidence of Adverse Experiences ≥ 1% Causal Relationship not Assessed		
	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

Additional adverse reactions occurring in < 1% of patients or subjects in domestic and/or international trials conducted with omeprazole, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

Body as a Whole

Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular

Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

Gastrointestinal

Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastroduodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic

Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional

Hyponatremia, hypoglycemia, and weight gain.

Musculoskeletal

Muscle cramps, myalgia, muscle weakness, joint pain, and leg pain.

Nervous System/Psychiatric

Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; and hemifacial dysesthesia.

Respiratory

Epistaxis, pharyngeal pain

Skin

Rash and rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, and hyperhidrosis.

Special Senses

Tinnitus, taste perversion

Ocular

Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.

Urogenital

Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.

Hematologic
Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.
The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.
Additional adverse reactions that could be caused by sodium bicarbonate, include metabolic alkalosis, seizures,and tetany.

OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. (See ADVERSE REACTIONS.) Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

In addition, a sodium bicarbonate overdose may cause hypocalcemia, hypokalemia, hypernatremia, and seizures.

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of omeprazole, is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks. (See INDICATIONS AND USAGE.)

Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

Preparation and Administration of Suspension

Zegerid should be taken on an empty stomach 1 hour before a meal.

Zegerid is supplied as unit dose packets containing an immediate release formulation of omeprazole 20 mg. Directions for use: Empty packet contents into a small cup containing 2 tablespoons of WATER. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

HOW SUPPLIED

Zegerid is a white, flavored powder packaged in individual 20 mg dose packets. It is supplied as follows:

NDC 68012-052-30 Cartons of 30: 20 mg unit dose packets

Storage

Store Zegerid in its original individual packets. Store at 25°C (68 - 77°F): excursions permitted to 15 - 30°C (59 - 86°F). [see **USP Controlled Room Temperature**]

Manufactured for: Santarus, Inc., San Diego, CA 92130
By: Patheon Inc., Whitby, Ontario L1N 5Z5

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/s/

Joyce Korvick
6/15/04 01:47:29 PM
for Dr. Robert Justice

tab 2

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(12) United States Patent
Phillips

(10) Patent No.: **US 6,489,346 B1**
(45) Date of Patent: ***Dec. 3, 2002**

(54) **SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHOD OF USING SAME**

(75) Inventor: **Jeffrey Owen Phillips**, Ashland, MO (US)

(73) Assignee: **The Curators of the University of Missouri**, Columbia, MO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/481,207**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/183,422, filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of application No. 08/680,326, filed on Jul. 15, 1996, now Pat. No. 5,840,737

(60) Provisional application No. 60/009,608, filed on Jan. 4, 1996.

(51) **Int. Cl.**[7] **C07D 401/12**; A61K 31/4439

(52) **U.S. Cl.** **514/338**; 514/395; 546/273.7; 548/307.1

(58) **Field of Search** 514/338, 395; 546/273.7; 548/307.1

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(57) **ABSTRACT**

There is provided a solid pharmaceutical composition in a dosage form that is not enteric-coated, having active ingredients including a non-enteric coated proton pump inhibitor and at least one buffering agent. The proton pump inhibitor is omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and the buffering agent is in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor. The dosage form includes a suspension tablet, a chewable tablet, an effervescent powder, or an effervescent tablet. Also provided is a method for treating an acid-related gastrointestinal disorder in a subject in need thereof by administering to the subject a solid pharmaceutical composition.

118 Claims, 2 Drawing Sheets

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FIG. 1

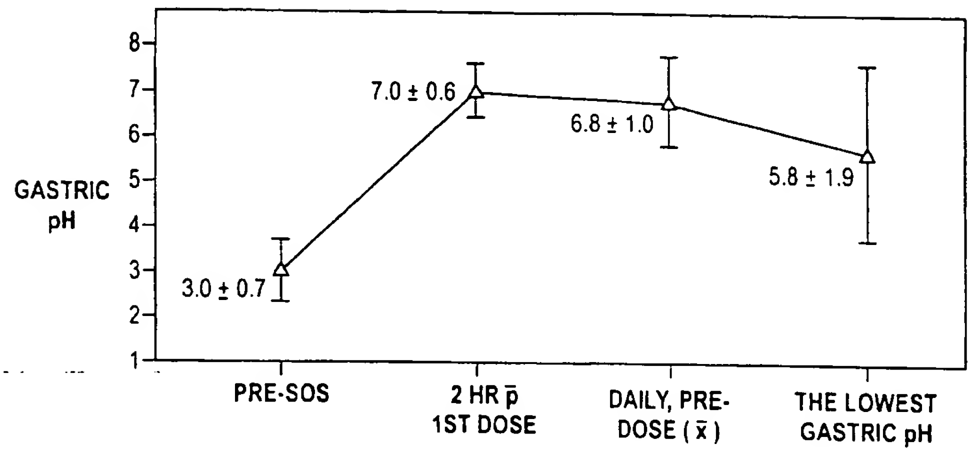

GASTRIC pH
8
7
6
5
4
3
2
1
7.0 ± 0.6
6.8 ± 1.0
5.8 ± 1.9
3.0 ± 0.7
PRE-SOS
2 HR p̄ 1ST DOSE
DAILY, PRE-DOSE (x̄)
THE LOWEST GASTRIC pH

FIG. 2

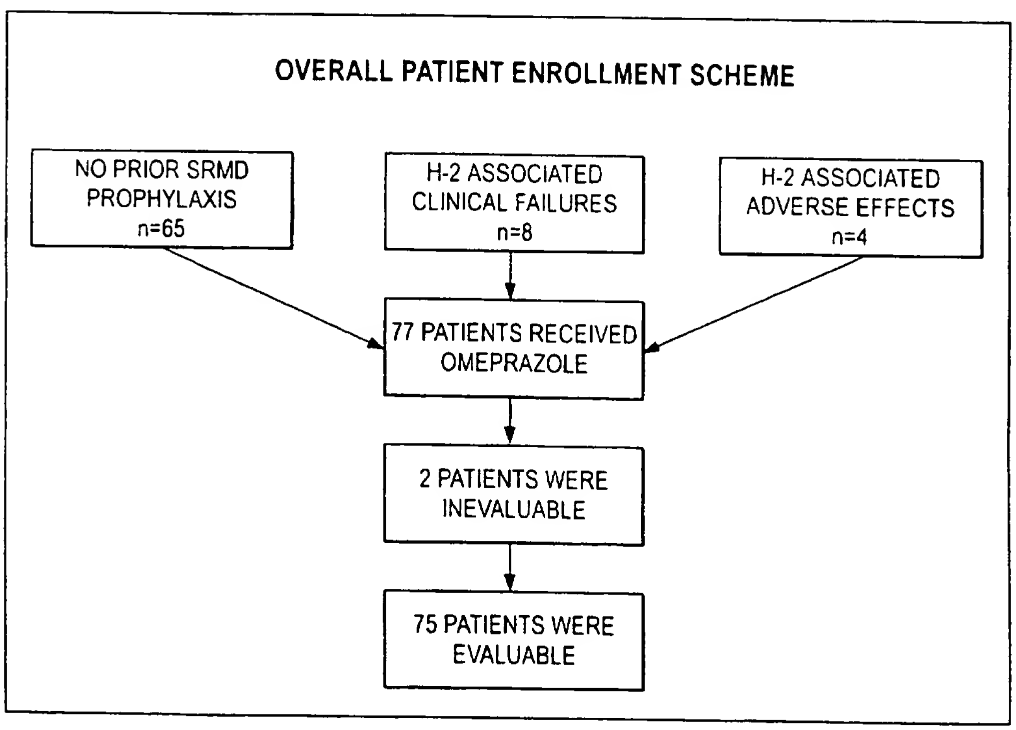

OVERALL PATIENT ENROLLMENT SCHEME
NO PRIOR SRMD PROPHYLAXIS n=65
H-2 ASSOCIATED CLINICAL FAILURES n=8
H-2 ASSOCIATED ADVERSE EFFECTS n=4
77 PATIENTS RECEIVED OMEPRAZOLE
2 PATIENTS WERE INEVALUABLE
75 PATIENTS WERE EVALUABLE

FIG. 3

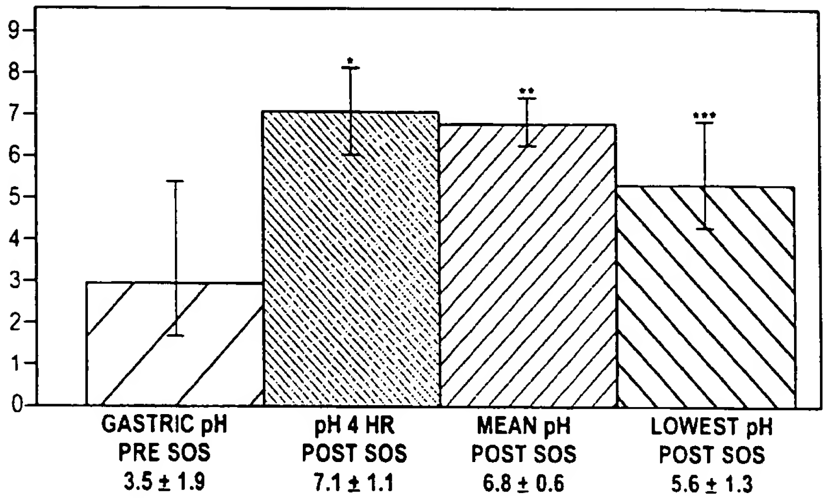
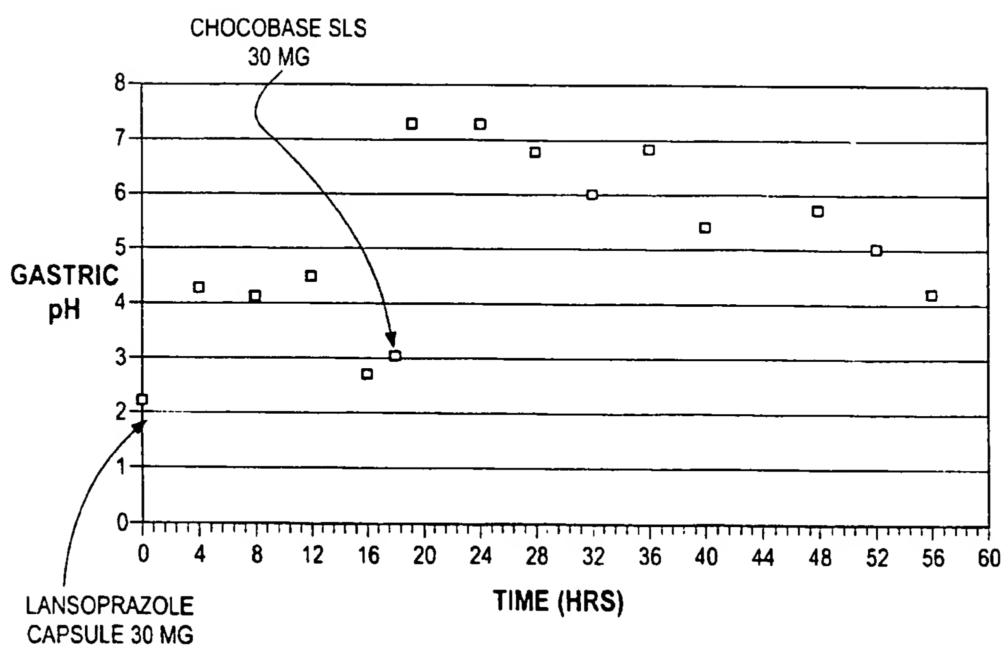

9
8
7
6
5
4
3
2
1
0
*
**
***
GASTRIC pH
PRE SOS
3.5 ± 1.9
pH 4 HR
POST SOS
7.1 ± 1.1
MEAN pH
POST SOS
6.8 ± 0.6
LOWEST pH
POST SOS
5.6 ± 1.3

FIG. 4


CHOCOBASE SLS
30 MG
GASTRIC
pH
8
7
6
5
4
3
2
1
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
TIME (HRS)
LANSOPRAZOLE
CAPSULE 30 MG

SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHOD OF USING SAME

This application is a continuation-in-part of U.S. patent application Ser. No. 09/183,422 filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/680,376 filed on Jul. 15, 1996, now U.S. Pat. No. 5,840,737, which claims priority to U.S. Provisional Application Serial No. 60/009,608 filed on Jan. 4, 1996. This application claims priority to all such previous applications, and such applications are hereby incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to pharmaceutical preparations comprising substituted benzimidazole proton pump inhibitors.

BACKGROUND OF THE INVENTION

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, that inhibits gastric acid secretion. Omeprazole belongs to a class of antisecretory compounds called proton pump inhibitors ("PPIs") that do not exhibit anticholinergic or H_2 histamine antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H^+, K^+-ATPase enzyme system (proton pump) at the secretory surface of the gastric parietal cell.

Typically, omeprazole, lansoprazole and other proton pump inhibitors are formulated in an enteric-coated solid dosage form (as either a delayed-release capsule or tablet) or as an intravenous solution (or as a product for reconstitution), and are prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. These above-listed conditions commonly arise in healthy or critically ill patients, and may be accompanied by significant upper gastrointestinal bleeding.

H_2-antagonists, antacids, and sucralfate are commonly administered to minimize the pain and the complications related to these conditions. These drugs have certain disadvantages associated with their use. Some of these drugs are not completely effective in the treatment of the aforementioned conditions and/or produce adverse side effects, such as mental confusion, constipation, diarrhea, and thrombocytopenia. H_2-antagonists, such as ranitidine and cimetidine, are relatively costly modes of therapy, particularly in NPO patients, which frequently require the use of automated infusion pumps for continuous intravenous infusion of the drug.

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, Pathogenesis, Diagnosis and Treatment of Acute Gastric Mucosa Lesions, Clin Gastroenterol 13: 635–650 (1984)). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., The Prevention of Gastrointestinal Tract Bleeding in Patients in an Intensive Care Unit, Surg. Gynecol. Obstet., 153: 214–220 (1981); Larson et al., Gastric Response to Severe Head Injury, Am. J. Surg. 147: 97–105 (1984); Czaja et al., Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History, N Engl. J. Med, 291: 925–929 (1974); Skillman et al., Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated with Lethal Hemorrhage From Acute Stress Ulceration, Am. J. Surg., 117: 523–530 (1969); and Cook et al., Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients, N. Engl. J. Med., 330:377–381 (1994)). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients, N. Engl. J. Med., 330:377–381 (1994)). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., Continuous Intravenous cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia, Crit. Care Med., 21: 19–39 ('1993)). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History, N Engl. J. Med, 291: 925–929 (1974); Peura and Johnson, Cimetidine for Prevention and Treatment of Gastroduodenal Mucosal Lesions in Patients in an Intensive Care Unit, Ann Intern Med., 103: 173–177 (1985)). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.

In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage and related complications is considered by many to be the standard of care (AMA Drug Evaluations). However, general consensus is lacking about which drugs to use in this setting (Martin et al., Continuous Intravenous Cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia, Crit. Care Med., 21: 19–39 (1993); Gafter et al., Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity with Cimetidine, Am. J. Gastroenterol, 64: 560–562 (1989) Martin et al., Stress Ulcers and Organ Failure in Intubated Patients in Surgical Intensive Care Units, Ann Surg., 215: 332–337 (1992)). In two recent meta-analyses (Cook et al., Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis, Am. J. Med., 91: 519–527 (1991); Tryba, Stress Ulcer Prophylaxis—Quo Vadis? Intens. Care Med. 20: 311–313 (1994)) Antacids, sucralfate, and H_2-antagonists were all found to be superior to placebo and similar to one another in preventing upper gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in fifteen to twenty percent of patients in which they are employed because of failure to prevent bleeding or control pH (Ostro et al., Control of Gastric pH With Cimetidire Boluses Versus Primed Infusions, Gastroenterology, 89: 532–537 (1985) Siepler, A Dosage Alternative for H-2 Receptor Antagonists, Continuous-Infusion, Clin. Ther., 8 (Suppl A): 24–33 (1986); Ballesteros et al., Bolus or Intravenous Infusion of Ranitidine: Effects on Gastric pH and Acid Secretion: A Comparison of Relative Cost and Efficacy, Ann. Intern. Med., 112:334–339 (1990)), or because of adverse effects (Gafter et al., Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity With Cimetidine, Am. J. Gastroenterol, 64: 560–562 (1989); Sax, Clinically Important Adverse Effects and Drug Interactions With H2-Receptor Antagonists: An Update, Pharmacotherapy 7(6 pt 2): 110S–115S (1987); Vial et al., Side Effects of Ranitidine, Drug Saf, 6:94–117(1991); Cantu and Korek,

Central Nervous System Reactions to Histamine-2 Receptor Blockers, Ann. Intern Med., 114: 1027–1034 (1991); and Spychal and Wickham, Thrombocytopenia Associated With Ranitidine, Br. Med. J., 291: 1687 (1985)). In addition, the characteristics of an ideal agent for the prophylaxis of stress gastritis were analyzed by Smythe and Zarowitz, Changing Perspectives of Stress Gastritis Prophylaxis, Ann Pharmacother, 28: 1073–1084 (1994) who concluded that none of the agents-currently in use fulfill their criteria.

Stress ulcer prophylaxis has become routine therapy in intensive care units in most hospitals (Fabian et al., Pneumonia and Stress Ulceration in Severely Injured Patients, Arch. Surg., 128: 185–191 (1993); Cook et al., Stress Ulcer Prophylaxis in the Critically Ill: A Meta-Analysis, Am. J. Med., 91: 519–527 (1991)). Controversy remains regarding pharmacologic intervention to prevent stress-related bleeding in critical care patients. It has been suggested that the incidence and risk of gastrointestinal bleeding has decreased in the last ten years and drug therapy may no longer be needed (Cook et al., Risk Factors for Gastrointestinal Bleeding in Critically Ill. Patients, N. Engl. J. Med., 330:377–381 (1994); Tryba, Stress Ulcer Propbylaxis—Quo Vadis? Intens. Care Med. 20: 311-313 (1994); Schepp, Stress Ulcer Prophylaxis.: Still a Valid Option in the 1990s?, Digestion 54: 189–199 (1993)). This reasoning is not supported by a recent placebo-controlled study. Martin. et al. conducted a prospective, randomized, double-blind, placebo-controlled comparison of continuous-infusion cimetidine and placebo for the prophylaxis of stress-related mucosal damage. The study was terminated early because of excessive bleeding-related mortality in the placebo group. It appears that the natural course of stress-related mucosal damage in a patient at risk who receives no prophylaxis remains significant. In the placebo group, thirty-three percent (33%) of patients developed clinically significant bleeding, nine percent (9%) required transfusion, and six percent (6%) died due to bleeding-related complications. In comparison, fourteen percent (14%) of cimetidine-treated patients developed clinically significant bleeding, six percent (6%) required transfusions, and one and one-half percent (1.5%) died due to bleeding-related complication. The difference in bleeding rates between treatment groups was statistically significant. This study clearly demonstrated that continuous-infusion cimetidine reduced morbidity in critical care patients. Although these data were used to support the approval of continuous-infusion cimetidine by the Food and Drug Administration for stress ulcer prophylaxis, H_2-antagonists fall short of being the optimal pharmacotherapeutic agents for preventing of stress-related mucosal bleeding.

Another controversy surrounding stress ulcer prophylaxis is which drug to use. In addition to the various H_2-antagonists, antacids and sucralfate are other treatment options for the prophylaxis of stress-related mucosal damage. An ideal drug in this setting should possess the following characteristics: prevent stress ulcers and their complications, be devoid of toxicity, lack drug interactions, be selective, have minimal associated costs (such as personnel time and materials), and be easy to administer (Smythe and Zarowitz, Changing Perspectives of Stress Gastritis Prophylaxis, Ann Pharmacother, 28: 1073–1084 (1994)). Some have suggested that sucralfate is possibly the ideal agent for stress ulcer prophylaxis (Smythe and Zarowitz, Changing Perspectives of Stress Gastritis Prophylaxis, Ann Pharmacother, 28: 1073–1084 (1994)). Randomized, controlled studies support the use of sucralfate (Borrero et al., Antacids vs. Sucralfate in Preventing Acute Gastrointestinal Tract Bleeding in Abdominal Aortic Aurgery, Arch. Surg., 121: 810–812 (1986); Tryba, Risk of Acute Stress Bleeding and Nosocomial Pneumonia in Ventilated Intensive Care Patients. Sucralfate vs. Antacids, Am. J. Med., 87(3B): 117–124 (1987); Cioffi et al., Comparison of Acid Neutralizing and Non-acid Neutralizing Stress Ulcer Prophylaxis in Thermally Injured Patients. J. Trauma, 36: 541–547 (1994); and Driks et al., Nosocomial Pneumonia in Intubated Patients Given Sucralfate as Compared With Antacids or Histamine Type 2 Blockers, N. Engl. J. Med., 317: 1376–1382 1987)), but data on critical care patients with head injury, trauma, or burns are limited. In addition, a recent study comparing sucralfate and cimetidine plus antacids for stress ulcer prophylaxis reported clinically significant bleeding in three of forty-eight (6%) sucralfate-treated patients, one of whom required a gastrectomy (Cioffi et al., Comparison of Acid Neutralizing and Non-acid Neutralizing Stress Ulcer Prophylaxis in Thermally Injured Patients, J. Trauma, 36: 541–547 (1994)). In the study performed by Driks and coworkers that compared sucralfate to conventional therapy (H_2-antagonists, antacids, or H_2-antagonists plus antacids), the only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm (Driks et al., Nosocomial Pneumonia in Intubated Patients Given Sucralfate as Compared With Antacids or Histamine Type 2 Blockers, N. Engl. J. Med., 317: 1376–1382(1987)).

H_2-antagonists fulfill many of the criteria for an ideal stress ulcer prophylaxis drug. Yet, clinically significant bleeds can occur during. H_2-antagonist prophylaxis (Martin et al., Continuous Intravenous Cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia, Crit. Care Med., 21: 19–39 (1993); Cook et al. , Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis, Am. J. Med., 91: 519–527 (1991); Schuman et al., Prophylactic Therapy for Acute Ulcer Bleeding: A Reappraisal, Ann Intern. Med, 106: 562–567 (1987)). Adverse events are not uncommon in the critical care population (Gafter et al., Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-Reactivity With Cimetidine, Am. J. Gastroenterol, 64: 560–562 (1989); Sax, Clinically Important Adverse Effects and Drug Interactions With H2-receptor Antagonists: An Update, Pharmacotherapy 7(6 pt 2): 110S–115S (1987); Vial et al., Side Effects of Ranitidine, Drug Saf., 6:94–117(1991); Cantu and Korek, Central Nervous System Reactions to Histamine-2 Receptor Blockers, Ann. Intern Med., 114: 1027–1034 (1991); Spychal and Wickham, Thrombocytopenia Associated With Ranitidine, Br. Med. J., 291: 1687 (1985)).

One reason proposed for the therapeutic H_2-antagonist failures is lack of pH control throughout the treatment period (Ostro et al., Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions, Gastroenterology, 89: 532–537 (1985)). Although the precise pathophysiologic mechanisms involved in stress ulceration are not clearly established, the high concentration of hydrogen ions in the mucosa (Fiddian-Green et al., 1987) or gastric fluid in contact with mucosal cells appears to be an important factor. A gastric pH >3.5 has been associated with a lower incidence of stress-related mucosal damage and bleeding (Larson et al., Gastric Response to Severe Head Injury, Am. J. Surg. 147: 97–105 (1984); Skillman et al., Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated With Lethal Hemorrhage From Acute Stress Ulceration, Am. J. Surg., 117: 523–530 (1969); Skillman et al., The Gastric Mucosal Barrier: Clinical and Experimental Studies in Critically Ill and Normal Man and in the Rabbit, Ann Surg., 172: 564–584 (1970); and Priebe and Skillman, Methods of Prophylaxis in Stress Ulcer Disease, World J. Surg., 5: 223–233 (1981)). Several studies have shown that H_2-antagonists, even in maximal doses, do not reliably or continuously increase intragastric pH above commonly targeted levels (3.5 to 4.5). This is true especially when used in fixed-dose bolus regimens (Ostro et al., Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions,

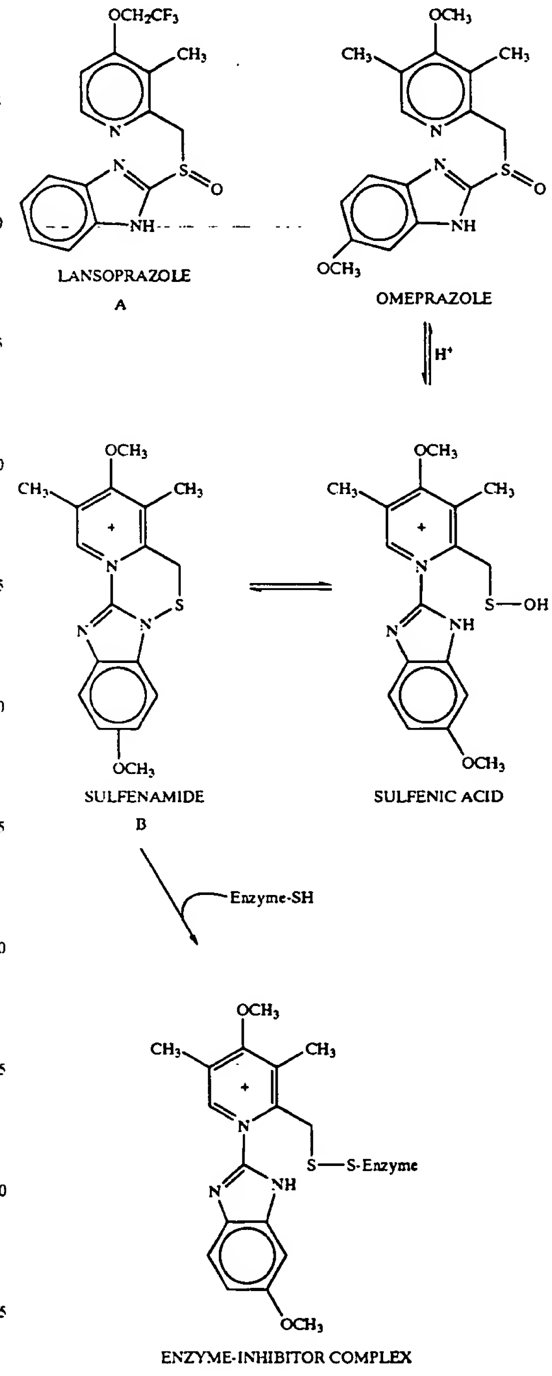
Gastroenterology, 89: 532–537 (1985); Siepler, A Dosage Alternative for H-2 Receptor Antagonists, Continuous-infusion, Clin. Ther., 8 (Suppl A): 24–33 (1986); Ballesteros et al., Bolus or Intravenous Infusion of Ranitidine: Effects on Gastric pH and Acid Secretion: A Comparison of Relative Cost and Efficacy, Ann. Intern. Med., 112:334–339 (1990)). In addition, gastric pH levels tend to trend downward with time when using a continuous-infusion of H_2-antagonists, which may be the result of tachyphylaxis (Ostro et al., Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions, Gastroenterology, 89: 532–537 (1985); Wilder-Smith and Merki, Tolerance During Dosing With H_2-receptor Antagonists. An Overview, Scand. J. Gastroenterol 27 (suppl. 193): 14–19 (1992)).

Because stress ulcer prophylaxis is frequently employed in the intensive care unit, it is essential from both a clinical and economic standpoint to optimize the pharmacotherapeutic approach. In an attempt to identify optimal therapy, cost of care becomes an issue. All treatment costs should be considered, including the costs of treatment failures and drug-related adverse events. While the actual number of failures resulting in mortality is low, morbidity (e.g., bleeding that requires blood transfusion) can be high, even though its association with the failure of a specific drug is often unrecognized.

Initial reports of increased frequency of pneumonia in patients receiving stress ulcer prophylaxis with agents that raise gastric pH has influenced the pharmacotherapeutic approach to management of critical care patients. However, several recent studies (Simms et al., Role of Gastric Colonization in the Development of Pneumonia in Critically Ill Trauma Patients: Results of a Prospective Randomized Trial, J. Trauma, 31: 531–536 (1991); Pickworth et al., Occurrence of Nasocomial Pneumonia in Mechanically Ventilated Trauma Patients: A Comparison of Sucralfate and Ranitidine, Crit. Care Med., 12: 1856–1862 (1993); Ryan et al., Nasocomial Pneumonia During Stress Ulcer Prophylaxis With Cimetidine and Sucralfate, Arch. Surg., 128: 1353–1357 (1993); Fabian et al., Pneumonia and Stress Ulceration in Severely Injured Patients, Arch. Surg., 128: 185–191 (1993)), a meta-analysis (Cook et al., Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis, Am. J. Med., 91: 519–527 (1991)), and a closer examination of the studies that initiated the elevated pH-associated pneumonia hypotheses (Schepp, Stress Ulcer Prophylaxis: Still a Valid Option in the 1990s?, Digestion 54: 189–199 (1993)) cast doubt on a causal relationship. The relationship between pneumonia and antacid therapy is much stronger than for H_2-antagonists. The shared effect of antacids and H_2-antagonists on gastric pH seems an irresistible common cause explanation for nosocomial pneumonia observed during stress ulcer prophylaxis. However, there are important differences between these agents that are not often emphasized (Laggner et al., Prevention of Upper Gastrointestinal Bleeding in Long-term Ventilated Patients, Am. J. Med., 86 (suppl 6A) : 81–84 (1989)). When antacids are exclusively used to control pH in the prophylaxis of stress-related upper gastrointestinal bleeding, large volumes are needed. Volume, with or without subsequent reflux, may be the underlying mechanism(s) promoting the development of pneumonia in susceptible patient populations rather than the increased gastric pH. The rate of pneumonia (12%) was not unexpected in this critical care population and compares with sucralfate, which does not significantly raise gastric pH (Pickworth et al., Occurrence of Nasocomial Pneumonia in Mechanically Ventilated Trauma Patients: A Comparison of Sucralfate and Ranitidine, Crit. Care Med., 12: 1856–1862 (1993); Ryan et al., Nasocomial Pneumonia During Stress Ulcer Prophylaxis With Cimetidine and Sucralfate, Arch. Surg., 128: 1353–1357 (1993)).

Omeprazole (Prilosec®), lansoprazole (Prevacid®) and other PPIs reduce gastric acid production by inhibiting H^+,K^+-ATPase of the parietal cell-the final common pathway for gastric acid secretion (Fellenius et al., Substituted Benzimidazoles Inhibit Gastric Acid Secretion by Blocking H^+,K^+-ATPase, Nature, 290: 159–161 (1981); Wallmark et al, The Relationship Between Gastric Acid Secretion and Gastric H^+,K^+-ATPase Activity, J. Biol. Chem., 260: 13681–13684 (1985); Fryklund et al., Function and Structure of Parietal Cells After H^+,K^+-ATPase Blockade, Am. J. Physiol., 254 (3 pt 1) ; G399–407 (1988)).

PPIs contain a sulfinyl group in a bridge between substituted benzimidazole and pyridine rings, as illustrated below.



At neutral pH, omeprazole, lansoprazole and other PPIs are chemically stable, lipid-soluble, weak bases that are devoid of inhibitory activity. These neutral weak bases reach parietal cells from the blood and diffuse into the secretory canaliculi, where the drugs become protonated and thereby trapped. The protonated agent rearranges to form a sulfenic acid and a sulfenamide. The sulfenamide interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane-spanning H^+,K^+-ATPase (Hardman et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics,* p. 907 (9th ed. 1996)). Omeprazole and lansoprazole, therefore, are prodrugs that must be activated to be effective. The specificity of the effects of PPIs is also dependent upon: (a) the selective distribution of H^+,K^+-ATPase; (b) the requirement for acidic conditions to catalyze generation of the reactive inhibitor; and (c) the trapping of the protonated drug and the cationic sulfenamide within the acidic canaliculi and adjacent to the target enzyme. (Hardman et al., 1996)).

Omeprazole and lansoprazole are available for oral administration as enteric coated particles in gelatin capsules. Other proton pump inhibitors such as rabeprazole and pantoprazole are supplied as enteric coated tablets. The enteric dosage forms of the prior art have been employed because it is very important that these drugs not be exposed to gastric acid prior to absorption. Although these drugs are stable at alkaline pH, they are destroyed rapidly as pH falls (e.g., by gastric acid). Therefore, if the microencapsulation or the enteric coating is disrupted (e.g., trituration to compound a liquid, or chewing the capsule), the drug will be exposed to degradation by the gastric acid in the stomach.

The absence of an intravenous or oral liquid dosage form in the United-States has limited the testing and use of omeprazole, lansoprazole and rabeprazole in the critical care patient population. Barie et al., Therapeutic Use of Omeprazole for Refractory Stress-induced Gastric Mucosal Hemorrhage, Crit. Care Med., 20: 899–901 (1992) have described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multi-organ failure. However, such pellets are not ideal as they can aggregate and occlude such tubes, and they are not suitable for patients who cannot swallow the pellets. Am J. Health-Syst Pharm 56:2327–30 (1999).

Proton pump inhibitors such as omeprazole represent an advantageous alternative to the use of H_2-antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage. However, in their current form (capsules containing enteric-coated granules or enteric-coated tablets), proton pump inhibitors can be difficult or impossible to administer to patients who are either unwilling or unable to swallow tablets or capsules, such as critically ill patients, children, the elderly, and patients suffering from dysphagia. Therefore, it would be desirable to formulate a proton pump inhibitor solution or suspension which can be enterally delivered to a patient thereby providing the benefits of the proton pump inhibitor without the drawbacks of the current enteric-coated solid dosage forms.

Omeprazole, the first proton pump inhibitor introduced into use, has been formulated in many different embodiments such as in a mixture of polyethylene glycols, adeps solidus and sodium lauryl sulfate in a soluble, basic amino acid to yield a formulation designed for administration in the rectum as taught by U.S. Pat. No. 5,219,870 to Kim.

U.S. Pat. No. 5,395,323 to Berglund ('323) discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient. The '323 patent teaches the use of an omeprazole tablet which is placed in the device and dissolved by normal saline, and infused parenterally into the patient. This device and method of parenteral infusion of omeprazole does not provide the omeprazole solution as an enteral product, nor is this omeprazole solution directly administered to the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate antacid effect of the present formulation..

U.S. Pat. No. 4,786,505 to Lovgren et al. discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH. The powder mixture is then formulated to small beads, pellets, tablets and may be loaded into capsules by conventional pharmaceutical procedures. This formulation of omeprazole does not provide an omeprazole dosage form which can be enterally administered to a patient who may be unable and/or unwilling to swallow capsules, tablets or pellets, nor does it teach a convenient form which can be used to make an omeprazole or other proton pump inhibitor solution or suspension.

Several buffered omeprazole oral solutions/suspensions have been disclosed. For example, Pilbrant et al., Development of an Oral Formulation of Omeprazole, Scand. J. Gastroent. 20 (Suppl. 108): 113–120 (1985) teaches the use of micronized omeprazole suspended in water, methylcellulose and sodium bicarbonate in a concentration of approximately 1.2 mg omeprazole/ml suspension.

Andersson et el., Pharmacokinetics of Various Single Intravenous and Oral Doses of Omeprazole, Eur J. Clin. Pharmacol. 39:, 195–197 (1990) discloses 10 mg, 40 mg, and 90 mg of oral omeprazole dissolved in PEG 400, sodium bicarbonate and water. The concentration of omeprazole cannot be determined as volumes of diluent are not disclosed. Nevertheless, it is apparent from this reference that multiple doses of sodium bicarbonate were administered with and after the omeprazole suspension.

Andersson et al., Pharmacokinetics and Bioavailability of Omeprazole After Single and Repeated Oral Administration in Healthy Subjects, Br. J. Clin. Pharmac. 29: 557–63 (1990) teaches the oral use of 20 mg of omeprazole, which was dissolved in 20 g of PEG 400 (sp. gravity=1.14) and diluted with 50 ml of sodium bicarbonate, resulting in a concentration of 0.3 mg/ml.

Regardh et al., The Pharmacokinetics of Omeprazole in Humans—A Study of Single Intravenous and Oral Doses, Ther. Drug Mon. 12: 163–72 (1990) discloses an oral dose of omeprazole at a concentration 0.4 mg/ml after the drug was dissolved in PEG 400, water and sodium bicarbonate.

Landahl et al., Pharmacokinetics Study of Omeprazole in Elderly Healthy Volunteers, Clin. Pharmacokinetics 23 (6): 469–476 (1992) teaches the use of an oral dose of 40 mg of omeprazole dissolved in PEG 400, sodium bicarbonate and water. This reference does not disclose the final concentrations utilized. Again, this reference teaches the multiple administration of sodium bicarbonate after the omeprazole solution.

Andersson et al., Pharmacokinetics of [^{14}C] Omeprazole in Patients with Liver Cirrhosis, Clin. Pharmacokinetics 24(1): 71–78 (1993) discloses the oral administration of 40 mg of omeprazole which was dissolved in PEG 400, water and sodium bicarbonate. This reference does not teach the final concentration of the omeprazole solution administered, although it emphasizes the need for concomitant sodium bicarbonate dosing to prevent acid degradation of the drug.

Nakagawa, et al., Lansoprazole: Phase I Study of lansoprazole (AG-1749) Anti-ulcer Agent, J. Clin. Therapeutics & Med. (1991) teaches the oral administration of 30 mg of lansoprazole suspended in 100 ml of sodium bicarbonate (0.3 mg/ml), which was administered to patients through a nasogastric tube.

All of the buffered omeprazole solutions described in these references were administered orally, and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration. In all of these studies, repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration. In the above-cited studies, as much as 48 mmoles of sodium bicarbonate in 300 ml of water must be ingested for a single dose of omeprazole to be orally administered.

The buffered omeprazole solutions of the above cited prior art require the ingestion of large amounts of sodium bicarbonate and large volumes of water by repeated administration. This has been considered necessary to prevent acid degradation of the omeprazole. In the above-cited studies, basically healthy volunteers, rather than sick patients, were given dilute buffered omeprazole utilizing pre-dosing and post-dosing with large volumes of sodium bicarbonate.

The administration of large amounts of sodium bicarbonate can produce at least six significant adverse effects, which can dramatically reduce the efficacy of the omeprazole in patients and reduce the overall health of the patients. First, the fluid volumes of these dosing protocols would not be suitable for sick or critically ill patients who must receive multiple doses of omeprazole. The large volumes would result in the distention of the stomach and increase the likelihood of complications in critically ill patients such as the aspiration of gastric contents.

Second, because bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their reflux disease as the belching can cause upward movement of stomach acid (Brunton, Agents for the Control of Gastric Acidity and Treatment of Peptic Ulcers, In, Goodman A G, et al. The Pharmacologic Basis of Therapeutics (New York, p. 907 (1990)).

Third, patients with conditions such as hypertension or heart failure are standardly advised to avoid the intake of excessive sodium as it can cause aggravation or exacerbation of their hypertensive conditions (Brunton, supra). The ingestion of large amounts of sodium bicarbonate is inconsistent with this advice.

Fourth, patients with numerous conditions that typically accompany critical illness should avoid the intake of excessive sodium bicarbonate as it can cause metabolic alkalosis that can result in a serious worsening of the patient's condition.

Fifth, excessive antacid intake (such as sodium bicarbonate) can result in drug interactions that produce serious adverse effects. For example, by altering gastric and urinary pH, antacids can alter rates of drug dissolution and absorption, bioavailability, and renal elimination (Brunton, supra).

Sixth, because the buffered omeprazole solutions of the prior art require prolonged administration of sodium bicarbonate, it makes it difficult for patients to comply with the regimens of the prior art. For example, Pilbrant. et al. disclose an oral omeprazole administration protocol calling for the administration to a subject who has been fasting for at least ten hours, a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later, the subject ingests a suspension of 60 mg of omeprazole in 50 ml of water that also contains 8 mmoles of sodium bicarbonate. This is rinsed down with another 50 ml of 8 mmoles sodium bicarbonate solution. Ten minutes after the ingestion of the omeprazole dose, the subject ingests 50 ml of bicarbonate solution (8 mmoles). This is repeated at twenty minutes and thirty minutes post omeprazole dosing to yield a total of 48 mmoles of, sodium bicarbonate and 300 ml of water in total which are ingested by the subject for a single omeprazole dose. Not only does this regimen require the ingestion of excessive amounts of bicarbonate and water, which is likely to be dangerous to some patients, it is unlikely that even healthy patients would comply with this regimen.

It is well documented that patients who are required to follow complex schedules for drug administration are non-compliant and, thus, the efficacy of the buffered omeprazole solutions of the prior art would be expected to be reduced due to non-compliance. Compliance has been found to be markedly reduced when patients are required to deviate from a schedule of one or two (usually morning and night) doses of a medication per day. The use of the prior art buffered omeprazole solutions which require administration protocols with numerous steps, different drugs (sodium bicarbonate+omeprazole+PEG 400 versus sodium bicarbonate alone), and specific time allotments between each stage of the total omeprazole regimen in order to achieve efficacious results is clearly in contrast with both current drug compliance theories and human nature.

The prior art (Pilbrant et al., 1985) teaches that the buffered omeprazole suspension can be stored at refrigerator temperatures for a week and deep frozen for a year while still maintaining 99% of its initial potency. It would be desirable to have an omeprazole or other proton pump inhibitor solution or suspension that could be stored at room temperature or in a refrigerator, for periods of time which exceed those of the prior art while still maintaining 99% of the initial potency. Additionally, it would be advantageous to have a form of the omeprazole and bicarbonate which can be utilized to instantly make the omeprazole solution/suspension of the present invention which is supplied in a solid form which imparts the advantages of improved shelf-life at room temperature, lower cost to produce, less expensive shipping costs, and which is less expensive to store.

It would, therefore, be desirable to have a proton pump inhibitor formulation, which provides a cost-effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonists, antacids, and sucralfate. Further, it would be desirable to have a proton pump inhibitor formulation which is convenient to prepare and administer to patients unable to ingest solid dosage forms such as tablets or capsules, which is rapidly absorbed, and can be orally or enterally delivered as a liquid form or solid form. It is desirable that the liquid formulation not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an antacid immediately upon delivery.

It would further be advantageous to have a potentiator or enhancer of the pharmacological activity of the PPIs. It has been theorized by applicant that the PPIs can only exert their effects on H^+,K^+-ATPase when the parietal cells are active. Accordingly, applicant has identified, as discussed below, parietal cell activators that are administered to synergistically enhance the activity of the PPIs.

Additionally, the intravenous dosage forms of PPIs of the prior art are often administered in larger doses than the oral forms. For example, the typical adult IV dose of omeprazole is greater than 100 mg/day whereas the adult oral dose is 20 to 40 mg/day. Large IV doses are necessary to achieve the

desired pharmacologic effect because, it is believed, many of the parietal cells are in a resting phase (mostly inactive) during an IV dose given to patients who are not taking oral substances by mouth (npo) and, therefore, there is little active (that which is inserted into the secretory canalicular membrane) H^+,K^+-ATPase to inhibit. Because of the clear disparity in the amount of drug necessary for IV versus oral doses, it would be very advantageous to have compositions and methods for IV administration where significantly less drug is required.

SUMMARY OF THE INVENTION AND ADVANTAGES

The foregoing advantages and objects are accomplished by the present invention. The present invention provides an oral solution/suspension comprising a proton pump inhibitor and at least one buffering agent. The PPI can be any substituted benzimidazole compound having H^+,K^+-ATPase inhibiting activity and being unstable to acid. Omeprazole and lansoprazole are the preferred PPIs for use in oral suspensions in concentrations of at least 1.2 mg/ml and 0.3 mg/ml, respectively. The liquid oral compositions can be further comprised of parietal cell activators, anti-foaming agents and/or flavoring agents.

The inventive composition can alternatively be formulated as a powder, tablet, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets and granules. Such dosage forms are advantageously devoid of any enteric coating or delayed or sustained-release delivery mechanisms, and comprise a PPI and at least one buffering agent to protect the PPI against acid degradation. Similar to the liquid dosage form, the dry forms can further include anti-foaming agents, parietal cell activators and flavoring agents.

Kits utilizing the inventive dry dosage forms are also disclosed herein to provide for the easy preparation of a liquid composition from the dry forms.

In accordance with the present invention, there is further provided a method of treating gastric acid disorders by administering to a patient a pharmaceutical composition comprising a proton pump inhibitor in a pharmaceutically acceptable carrier and at least one buffering agent wherein the administering step comprises providing a patient with a single dose of the composition without requiring further administering of the buffering agent.

Additionally, the present invention relates to a method for enhancing the pharmacological activity of an intravenously administered proton pump inhibitor in which at least one parietal cell activator is orally administered to the patient before, during and/or after the intravenous administrations of the proton pump inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

FIG. 1 is a graph showing the effect of the omeprazole solution of the present invention on gastric pH in patients at risk for upper gastrointestinal bleeding from stress-related mucosal damage;

FIG. 2 is a flow chart illustrating a patient enrollment scheme;

FIG. 3 is a bar graph illustrating gastric pH both pre- and post-administration of omeprazole solution according to the present invention; and

FIG. 4 is a graph illustrating the stomach pH values after the oral administration of both chocolate plus lansoprazole and lansoprazole alone.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention relates to a pharmaceutical composition comprising a proton pump inhibitor and a buffering agent with or without one or more parietal cell activators. While the present invention may be embodied in many different forms, several specific embodiments are discussed herein with the understanding that the present disclosure is to be considered only as an exemplification of the principles of the invention, and it is not intended to limit the invention to the embodiments illustrated.

For the purposes of this application, the term "proton pump inhibitor" (PPI) shall mean any substituted benzimidazole possessing pharmacological activity as an inhibitor of H^+,K^+-ATPase, including, but not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, perprazole (s-omeprazole magnesium), habeprazole, ransoprazole, pariprazole, and leminoprazole in neutral form or a salt form, a single enantiomer or isomer or other derivative or an alkaline salt of an enantiomer of the same.

The inventive composition comprises dry formulations, solutions and/or suspensions of the proton pump inhibitors. As used herein, the terms "suspension" and "solution" are interchangeable with each other and mean solutions and/or suspensions of the substituted benzimidazoles.

After absorption of the PPI (or administration intravenously) the drug is delivered via the bloodstream to various tissues and cells of the body including the parietal cells. Research suggests that the PPI is in the form of a weak base and is non-ionized and thereby freely passes through physiologic membranes, including the cellular membranes of the parietal cell. It is believed that the non-ionized PPI moves into the acid-secreting portion of the parietal cell, the secretory canaliculus. Once in the acidic millieu of the secretory canaliculus, the PPI is apparently protonated (ionized) and converted to the active form of the drug. Generally, ionized proton pump inhibitors are membrane impermeable and form disulfide covalent bonds with cysteine residues in the alpha subunit of the proton pump.

The inventive pharmaceutical composition comprising a proton pump inhibitor such as omeprazole, lansoprazole or other proton pump inhibitor and derivatives thereof can be used for the treatment or prevention of gastrointestinal conditions including, but not limited to, active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison Syndrome. Treatment of these conditions is accomplished by administering to a patient an effective amount of the pharmaceutical composition according to the present invention.

The proton pump inhibitor is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. The term "effective amount" means, consistent with considerations known in the art, the amount of PPI or other agent effective to achieve a pharmacologic effect or therapeutic improvement without undue adverse side effects, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood transfusion, improved survival rate, more rapid recovery, parietal cell activation and H^+,K^+-ATPase inhibition or improvement or elimination of symptoms, and other indicators as are selected as appropriate measures by those skilled in the art.

The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range from approximately <2 mg/day to

approximately 300 mg/day. The standard approximate daily oral dosage is typically 20 mg of omeprazole, 30 mg lansoprazole, 40 mg pantoprazole, 20 mg rabeprazole, and the pharmacologically equivalent doses of the following PPIs: habeprazole, pariprazole, dontoprazole, ransoprazole, perprazole (s-omeprazole magnesium), and leminoprazole.

A pharmaceutical formulation of the proton pump inhibitors utilized in the present invention can be administered orally or enterally to the patient. This can be accomplished, for example, by administering the solution via a nasogastric (ng) tube or other indwelling tubes placed in the GI tract. In order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the PPI solution of the present invention is administered in a single dose which does not require any further administration of bicarbonate, or large amounts of bicarbonate, or other buffer following the administration of the PPI solution, nor does it require a large amount of bicarbonate or buffer in total. That is, unlike the prior art PPI solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose which does not require administration of bicarbonate either before or after administration of the PPI. The present invention eliminates the need to pre-or post-dose with additional volumes of water and sodium bicarbonate. The amount of bicarbonate administered via the single dose administration of the present invention is less than the amount of bicarbonate administered as taught in the prior art references cited above.

Preparation of Oral Liquids

The liquid oral pharmaceutical composition of the present invention is prepared by mixing omeprazole (Prilosec® AstraZeneca) or other proton pump inhibitor or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). Preferably, omeprazole or other proton pump inhibitor, which can be obtained from a capsule or tablet or obtained from the solution for parenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other PPI) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0 mg/ml. The preferred concentration for the omeprazole in the solution ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml, with 2.0 mg/ml being the standard concentration. For lansoprazole (Prevacid® TAP Pharmaceuticals, Inc.) the concentration can range from about 0.3 mg/ml to 10 mg/ml with the preferred concentration being about 3 mg/ml.

Although sodium bicarbonate is the preferred buffering agent employed in the present invention to protect the PPI against acid degradation, many other weak and strong bases (and mixtures thereof) can be utilized. For the purposes of this application, "buffering agent" shall mean any pharmaceutically appropriate weak base or strong base (and mixtures thereof) that, when formulated or delivered with (e.g., before, during and/or after) the PPI, functions to substantially prevent or inhibit the acid degradation of the PPI by gastric acid sufficient to preserve the bioavailability of the PPI administered. The buffering agent is administered in an amount sufficient to substantially achieve the above functionality. Therefore, the buffering agent of the present invention, when in the presence of gastric acid, must only elevate the pH of the stomach sufficiently to achieve adequate bioavailability of the drug to effect therapeutic action.

Accordingly, examples of buffering agents include, but are not limited to, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate coprecipitate, a mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium cholride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts.

The pharmaceutically acceptable carrier of the oral liquid preferably comprises a bicarbonate salt of Group IA metal as buffering agent, and can be prepared by mixing the bicarbonate salt of the Group IA metal, preferably sodium bicarbonate, with water. The concentration of the bicarbonate salt of the Group IA metal in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt of the Group IA metal ranges from approximately 7.5 percent to approximately 10.0 percent. In a preferred embodiment of the present invention, sodium bicarbonate is the preferred salt and is present in a concentration of approximately 8.4 percent.

More specifically, the amount of sodium bicarbonate 8.4% used in the solution of the present invention is approximately 1 mEq (or mmole) sodium bicarbonate per 2 mg omeprazole, with a range of approximately 0.2 mEq (mmole) to 5 mEq (mmole) per 2 mg of omeprazole.

In a preferred embodiment of the present invention, enterically-coated omeprazole particles are obtained from delayed release capsules (Prilosec® AstraZeneca). Alternatively, omeprazole powder can be used. The enterically coated omeprazole particles are mixed with a sodium bicarbonate ($NaHCO_3$) solution (8.4%), which dissolves the enteric coating and forms an omeprazole solution. The omeprazole solution has pharmacokinetic advantages over standard time-released omeprazole capsules, including: (a) more rapid drug absorbance time (about 10 to 60 minutes) following administration for the omeprazole solution versus about 1 to 3 hours following administration for the enteric-coated pellets; (b) the $NaHCO_3$ solution protects the omeprazole from acid degradation prior to absorption; (c) the $NaHCO_3$ acts as an antacid while the omeprazole is being absorbed; and (d) the solution can be administered through an existing indwelling tube without clogging, for example, nasogastric or other feeding tubes (jejunal or duodenal), including small bore needle catheter feeding tubes.

Additionally, various additives can be incorporated into the inventive solution to enhance its stability, sterility and isotonicity. Further, antimicrobial preservatives, antioxidants, chelating agents, and additional buffers can be added, such as ambicin. However, microbiological evidence shows that this formulation inherently possesses antimicrobial and antifungal activity. Various antibacterial and antifungal agents such as, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like can enhance prevention of the action of microorganisms.

In many cases, it would be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Additionally, thickening agents such as methylcellulose are desirable to use in order to reduce the settling of the omeprazole or other PPI or derivatives thereof from the suspension.

The liquid oral solution may further comprise flavoring agents (e.g., chocolate, root beer or watermelon) or other flavorings stable at pH 7 to 9, anti-foaming agents (e.g.,

simethicone 80 mg, Mylicon®) and parietal cell activators (discussed below).

The present invention further includes a pharmaceutical composition comprising omeprazole or other proton pump inhibitor and derivatives thereof and at least one buffering agent in a form convenient for storage, whereby when the composition is placed into an aqueous solution, the composition dissolves yielding a suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution or suspension in an aqueous solution. The omeprazole or other PPIs and buffering agent can be formed into a tablet, capsule, pellets or granules, by methods well known to those skilled in the art.

The resultant omeprazole solution is stable at room temperature for several weeks and inhibits the growth of bacteria or fungi as shown in Example X below. Indeed, as established in Example XIII, the solution maintains greater than 90% of its potency for 12 months. By providing a pharmaceutical composition including omeprazole or other PPI with buffer in a solid form, which can be later dissolved or suspended in a prescribed amount of aqueous solution to yield the desired concentration of omeprazole and buffer, the cost of production, shipping, and storage are greatly reduced as no liquids are shipped (reducing weight and cost), and there is no need to refrigerate the solid form of the composition or the solution. Once mixed the resultant solution can then be used to provide dosages for a single patient over a course of time, or for several patients.

Tablets and Other Solid Dosage Forms

As mentioned above, the formulations of the present invention can also be manufactured in concentrated forms, such as tablets, suspension tablets and effervescent tablets or powders, such that upon reaction with water or other diluent, the aqueous form of the present invention is produced for oral, enteral or parenteral administration.

The present pharmaceutical tablets or other solid dosage forms disintegrate rapidly in aqueous media and form an aqueous solution of the PPI and buffering agent with minimal shaking or agitation. Such tablets utilize commonly available materials and achieve these and other desirable objectives. The tablets or other solid dosage forms of this invention provide for precise dosing of a PPI that may be of low solubility in water. They are particularly useful for medicating children and the elderly and others in a way that is much more acceptable than swallowing or chewing a tablet. The tablets that are produced have low friability, making them easily transportable.

The term "suspension tablets" as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the PPI. The suspension tablets of this invention comprise, in combination, a therapeutic amount of a PPI, a buffering agent, and a disintegrant. More particularly, the suspension tablets comprise about 20 mg omeprazole and about 1–20 mEq of sodium bicarbonate.

Croscarmellose sodium is a known disintegrant for tablet formulations, and is available from FMC Corporation, Philadelphia, Pa. under the trademark Ac-Di-Sol®. It is frequently blended in compressed tableting formulations either alone or in combination with microcrystalline cellulose to achieve rapid disintegration of the tablet.

Microcrystalline cellulose, alone or coprocessed with other ingredients, is also a common additive for compressed tablets and is well known for its ability to improve compressibility of difficult to compress tablet materials. It is commercially available under the Avicel® trademark. Two different Avicel® products are utilized, Avicel® PH which is microcrystalline cellulose, and Avicel® AC-815, a coprocessed spray dried residue of microcrystalline cellulose and a calcium, sodium alginate complex in which the calcium to sodium ratio is in the range of about 0.40:1 to about 2.5:1. While AC-815 is comprised of 85% microcrystalline cellulose (MCC) and 15% of a calcium, sodium alginate complex, for purposes of the present invention this ratio may be varied from about 75% MCC to 25% alginate up to about 95% MCC to 5% alginate. Depending on the particular formulation and active ingredient, these two components may be present in approximately equal amounts or in unequal amounts, and either may comprise from about 10% to about 50% by weight of the tablet.

The suspension tablet composition may, in addition to the ingredients described above, contain other ingredients often used in pharmaceutical tablets, including flavoring agents, sweetening agents, flow aids, lubricants or other common tablet adjuvants, as will be apparent to those skilled in the art. Other disintegrants, such as crospbvidone and sodium starch glycolate may be employed, although croscarmellose sodium is preferred.

In addition to the suspension tablet, the solid formulation of the present invention can be in the form of a powder, a tablet, a capsule, or other suitable solid dosage form (e.g., a pelleted form or an effervescing tablet, troche or powder), which creates the inventive solution in the presence of diluent or upon ingestion. For example, the water in the stomach secretions or water which is used to swallow the solid dosage form can serve as the aqueous diluent.

Compressed tablets are solid dosage forms prepared by compacting a formulation containing an active ingredient and excipients selected to aid the processing and improve the properties of the product. The term "compressed tablet" generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression or by pre-compaction tapping followed by a final compression.

Such solid forms can be manufactured as is well known in the art. Tablet forms can include, for example, one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmaceutically compatible carriers. The manufacturing processes may employ one, or a combination of, four established methods: (1) dry mixing; (2) direct compression; (3) milling; and (4) non-aqueous granulation. Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Such tablets may also comprise film coatings, which preferably dissolve upon oral ingestion or upon contact with diluent.

Non-limiting examples of buffering agents which could be utilized in such tablets include sodium bicarbonate, alkali earth metal salts such as calcium carbonate, calcium hydroxide, calcium lactate, calcium glycerophosphate, calcium acetate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide. A particular alkali earth metal salt useful for making an antacid tablet is calcium carbonate.

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An example of a low density alkali earth metal salt useful for making the granules according to the present invention is extra light calcium carbonate available from Specialty Minerals Inc., Adams, Me. The density of the extra light calcium carbonate, prior to being processed according to the present invention, is about 0.37 gm/ml.

The granules used to make the tablets according to one embodiment of the present invention are made by either spray drying or pre-compacting the raw materials. Prior to being processed into granules by either process, the density

of the alkali earth metal salts useful in the present invention ranges from about 0.3 gm/ml to about 0.55 gm/ml, preferably about 0.35 gm/ml to about 0.45 gm/ml, even more preferably about 0.37 gm/ml to about 0.42 gm/ml.

Additionally, the present invention can be manufactured by utilizing micronized compounds in place of the granules or powder. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate. Although micronization results in increased surface area possibly causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole and other proton pump inhibitors.

The present invention also relates to administration kits to ease mixing and administration. A month's supply of powder or tablets, for example, can be packaged with a separate month's supply of diluent, and a re-usable plastic dosing cup. More specifically, the package could contain thirty (30) suspension tablets containing 20 mg omeprazole each, 1 L sodium bicarbonate 8.4% solution, and a 30 ml dose cup. The user places the tablet in the empty dose cup, fills it to the 30 ml mark with the sodium bicarbonate, waits for it to dissolve (gentle stirring or agitation may be used), and then ingests the suspension. One skilled in the art will appreciate that such kits may contain many different variations of the above components. For example, if the tablets or powder are compounded to contain PPI and buffering agent, the diluent may be water, sodium bicarbonate, or other compatible diluent, and the dose cup can be larger than 30 ml in size. Also, such kits can be packaged in unit dose form, or as weekly, monthly, or yearly kits, etc.

Although the tablets of this invention are primarily intended as a suspension dosage form, the granulations used to form the tablet may also be used to form rapidly disintegrating chewable tablets, lozenges, troches, or swallowable tablets. Therefore, the intermediate formulations as well as the process for preparing them provide additional novel aspects of the present invention.

Effervescent tablets and powders are also prepared in accordance with the present invention. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and tartaric acid. When the salts are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence."

The choice of ingredients for effervescent granules. depends both upon the requirements of the manufacturing process and the necessity of making a preparation which dissolves readily in water. The two required ingredients are at least one acid and at least one base. The base releases carbon dioxide upon reaction with the acid. Examples of such acids include, but are not limited to, tartaric acid and citric acid. Preferably, the acid is a combination of both tartaric acid and citric acid. Examples of bases include, but are not limited to, sodium carbonate, potassium bicarbonate and sodium bicarbonate. Preferably, the base is sodium bicarbonate, and the effervescent combination has a pH of about 6.0 or higher.

Effervescent salts preferably include the following ingredients, which actually produce the effervescence: sodium bicarbonate, citric acid and tartaric acid. When added to water the acids and base react to liberate carbon dioxide, resulting in effervescence. It should be noted that any acid-base combination which results in the liberation of carbon dioxide could be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use, and result in a pH of about 6.0 or higher.

It should be noted that it requires 3 molecules of $NaHCO_3$ (sodium bicarbonate) to neutralize 1 molecule of citric acid and 2 molecules of $NaHCO_3$ to neutralize 1 molecule of tartaric acid. It is desired that the approximate ratio of ingredients is as follows Citric Acid:Tartaric Acid:Sodium Bicarbonate=1:2:3.44 (by weight). This ratio can be varied and continue to produce an effective release of carbon dioxide. For example, ratios of about 1:0:3 or 0:1:2 are also effective.

The method of preparation of the effervescent granules of the present invention employs three basic processes: wet and dry granulation, and fusion. The fusion method is used for the preparation of most commercial effervescent powders. It should be noted that although these methods are intended for the preparation of granules, the formulations of effervescent salts of the present invention could also be prepared as tablets, according to well known prior art technology for tablet preparation.

Wet granulation is the oldest method of granule preparation. The individual steps in the wet granulation process of tablet preparation include milling and sieving of the ingredients; dry powder mixing; wet massing; granulation; and final grinding.

Dry granulation involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty rotary tablet press. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillation granulator. The individual steps include mixing of the powders; compressing (slugging); and grinding (slug reduction or granulation). No wet binder or moisture is involved in any of the steps.

The fusion method is the most preferred method for preparing the granules of the present invention. In this method, the compressing (slugging) step of the dry granulation process is eliminated. Instead, the powders are heated in an oven or other suitable source of heat.

PPIs Administered with Parietal Cell Activators

Applicant has unexpectedly discovered that certain compounds, such as chocolate, calcium and sodium bicarbonate and other alkaline substances, stimulate the parietal cells and enhance the pharmacologic activity of the PPI administered. For the purposes of this application, "parietal cell activator" shall mean any compound or mixture of compounds possessing such stimulatory effect including, but not limited to, chocolate, sodium bicarbonate, calcium (e.g., calcium carbonate, calcium gluconate, calcium hydroxide, calcium acetate and calcium glycerophosphate), peppermint oil, spearmint oil, coffee, tea and colas (even if decaffeinated), caffeine, theophylline, theobromine, and amino acids (particularly aromatic amino acids such as phenylalanine and tryptophan) and combinations thereof and the salts thereof.

Such parietal cell activators are administered in an amount sufficient to produce the desired stimulatory effect without causing untoward side effects to patients. For example, chocolate, as raw cocoa, is administered in an amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of other PPI). The dose of activator administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response (i.e., enhanced effect of PPI) over a reasonable time frame. The dose will be determined by the strength of the particular compositions employed and the condition of the person, as well as the body weight of the person to be treated. The size of the dose

also will be determined by the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular composition.

The approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other PPI) are:

Chocolate (raw cocoa)—5 mg to 2.5 g
Sodium bicarbonate—7 mEq to 25 mEq
Calcium carbonate—1 mg to 1.5 Gm
Calcium gluconate—1 mg to 1.5 Gm
Calcium lactate—1 mg to 1.5 Gm
Calcium hydroxide—1 mg to 1.5 Gm
Calcium acetate—0.5 mg to 1.5 Gm
Calcium glycerophosphate—0.5 mg to 1.5 Gm
Peppermint oil—(powdered form) 1 mg to 1 Gm
Spearmint oil—(powdered form) 1 mg to 1 Gm
Coffee—20 ml to 240 ml
Tea—20 ml to 240 ml
Cola—20 ml to 240 ml
Caffeine—0.5 mg to 1.5 GM
Theophylline—0.5 mg to 1.5 GM
Theobromine—0.5 mg to 1.5 GM
Phenylalanine—0.5 mg to 1.5 GM
Tryptophan—0.5 mg to 1.5 GM

Pharmaceutically acceptable carriers are well-known to those who are skilled in the art. The choice of carrier will be determined, in part, both by the particular composition and by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical compositions of the present invention.

EXAMPLE I

A. Fast Disintegrating Suspension Tablets of Omeprazole

A fast disintegrating tablet is compounded as follows: Croscarmellose sodium 300 g is added to the vortex of a rapidly stirred beaker containing 3.0 kg of deionized water. This slurry is mixed for 10 minutes. Omeprazole 90 g (powdered) is placed in the bowl of a Hobart mixer. After mixing, the slurry of croscarmellose sodium is added slowly to the omeprazole in the mixer bowl, forming a granulation which is then placed in trays and dried at 70° C. for three hours. The dry granulation is then placed in a blender, and to it is added 1,500 g of Avicel® AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 1,500 g of Avicel® PH-302 (microcrystalline cellulose). After this mixture is thoroughly blended, 35 g of magnesium stearate is added and mixed for 5 minutes. The resulting mixture is compressed into tablets on a standard tablet press (Hata HS). These tablets have an average weight of about 1.5 g, and contain about 20 mg omeprazole. These tablets have low friability and rapid disintegration time. This formulation may be dissolved in an aqueous solution containing a buffering agent for immediate oral administration.

Alternatively, the suspension tablet may be swallowed whole with a solution of buffering agent. In both cases, the preferred solution is sodium bicarbonate 8.4%. As a further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other PPI) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole with an aqueous diluent.

B. 10 mg Tablet Formula

Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg

C. 20 mg Tablet Formula

Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg

D. Tablet for Rapid Dissolution

Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Croscarmellose sodium	12 mg

E. Powder for Reconstitution for Oral Use (or per ng tube).

Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Glycerine	200 g

F. 10 mg Tablet Formula

Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	1 mg
Magnesium stearate	1 mg

G. 10 mg Tablet Formula

Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	200 mg
Calcium glycerophosphate	200 mg
Sodium bicarbonate	400 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg

EXAMPLE II

Standard Tablet of PPI and Buffering Agent

Ten (10) tablets were prepared using a standard tablet press, each tablet comprising about 20 mg omeprazole and about 975 mg sodium bicarbonate uniformly dispersed throughout the tablet. To test the dissolution rate of the tablets, each was added to 60 ml of water. Using previously prepared liquid omeprazole/sodium bicarbonate solution as a visual comparator, it was observed that each tablet was completely dispersed in under three (3) minutes.

Another study using the tablets compounded according to this Example evaluated the bioactivity of the tablets in five (5) adult critical care patients. Each subject was administered one tablet via ng with a small amount of water, and the pH of ng aspirate was monitored using paper measure. The pH for each patient was evaluated for 6 hours and remained above 4, thus demonstrating the therapeutic benefit of the tablets in these patients.

Tablets were also prepared by boring out the center of sodium bicarbonate USP 975 mg tablets with a knife. Most of the removed sodium bicarbonate powder was then triturated with the contents of a 20 mg Prilosec® capsule and the resulting mixture was then packed into the hole in the tablet and sealed with glycerin.

EXAMPLE III

PPI Central Core Tablet

Tablets are prepared in a two-step process. First, about 20 mg of omeprazole is formed into a tablet as is known in the art to be used as a central core. Second, about 975 mg sodium bicarbonate USP is used to uniformly surround the central core to form an outer protective cover of sodium bicarbonate. The central core and outer cover are both prepared using standard binders and other excipients to create a finished, pharmaceutically acceptable tablet.

EXAMPLE IV

Effervescent Tablets and Granules

The granules of one 20 mg Prilosec® capsule were emptied into a mortar and triturated with a pestle to a fine powder. The omeprazole powder was then geometrically diluted with about 958 mg sodium bicarbonate USP, about 832 mg citric acid USP and about 312 mg potassium carbonate USP to form a homogeneous mixture of effervescent omeprazole powder. This powder was then added to about 60 ml of water whereupon the powder reacted with the water to create effervescence. A bubbling solution resulted of omeprazole and principally the antacids sodium citrate and potassium citrate. The solution was then administered orally to one adult male subject and gastric pH was measured using pHydrion paper. The results were as follows:

Time Interval	pH Measured
Immediately prior to dose	2
1 hour-post dose	7
2 hours post dose	6
4 hours post dose	6
6 hours post dose	5
8 hours post dose	4

One skilled in the art of pharmaceutical compounding will appreciate that bulk powders can be manufactured using the above ratios of ingredients, and that the a powder can be pressed into tablets using standard binders and excipients. Such tablets are then mixed with water to activate the effervescent agents and create the desired solution. In addition, lansoprazole 30 mg (or an equipotent dose of other PPI) can be substituted for omeprazole.

The effervescent powder and tablets can alternatively be formulated by employing the above mixture but adding an additional 200 mg of sodium bicarbonate USP to create a resulting solution with a higher pH. Further, instead of the excess 200 mg of sodium bicarbonate, 100 mg of calcium glycerophosphate or 100 mg of calcium lactate can be employed. Combinations of the same can also added.

EXAMPLE V

Parietal Cell Activator "Choco-Base™" Formulations and Efficacy

Children are affected by gastroesophageal reflux disease (GERD) with atypical manifestations. Many of these atypical symptoms are difficult to control with traditional drugs such as H_2-antagonists, cisapride, or sucralfate. PPIs are more effective in controlling gastric pH and the symptoms of GERD than other agents. However, PPIs are not available in dosage forms that are easy to administer to young children. To address this problem, applicant employed omeprazole or lansoprazole in a buffered chocolate suspension (Choco-Base, in children with manifestations of GERD.

Applicant performed a retrospective evaluation of children with GERD referred to the University of Missouri-Columbia from 1995 to 1998 who received treatment with the experimental omeprazole or lansoprazole Choco-Base suspension formulated in accordance with Formulation 1 stated below. Data were included on all patients with follow up information sufficient to draw conclusions about pre/post treatment (usually >6 months). There were 25 patients who met the criteria for this evaluation. Age range was several weeks to greater than 5 years. Most patients had a history of numerous unsuccessful attempts at ameliorating the effects of GERD. Medication histories indicated many trials of various drugs.

The primary investigator reviewed all charts for uniformity of data collection. When insufficient data was available in the University charts, attempts were made to review

charts in the local primary care physicians' offices for follow-up data. If information was still unavailable to review, attempts were made to contact family for follow-up. If data were still unavailable the patients were considered inevaluable.

Patient charts were reviewed in detail. Data noted were date of commencement of therapy, date of termination of therapy and any reason for termination other than response to treatment. Patient demographics were also recorded, as were any other medical illnesses. Medical illnesses were divided grossly into those that are associated with or exacerbate GERD and those that do not.

Patient charts were examined for evidence of response to therapy. As this was largely a referral population, and a retrospective review, quantification of symptomatology based on scores, office visits and ED visits was difficult. Therefore, applicant examined charts for evidence of an overall change in patient symptoms. In specific, any data to point towards improvement, decline or lack of change were examined and recorded.

Results.

A total of 33 pediatric patients to date have been treated with the above-described suspension at the University of Missouri—Columbia. Of the 33 patients, 9 were excluded from the study, all based upon insufficient data about commencement, duration or outcome in treatment with PPI therapy. This left 24 patients with enough data to draw conclusions.

Of the 24 remaining patients, 18 were males and 6 females. Ages at implementation of PPI therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months [mean of 37 mo.] Early on, reflux was usually documented by endoscopy and confirmed by pH probe. Eventually, pH probe was dropped and endoscopy was the sole method for documenting reflux, usually at the time of another surgery (most often T-tubes or adenoidectomy). Seven patients had pH probe confirmation of GERD, whereas 18 had endoscopic confirmation of reflux including all eight. who had pH probing done (See Graphs 1 and 2 below). Reflux was diagnosed on endoscopy most commonly by cobblestoning of the tracheal wall, with laryngeal and pharyngeal cobblestoning as findings in a few patients. Six patients had neither pH nor endoscopic documentation of GERD, but were tried on PPI therapy based on symptomatology alone.

Past medical history was identified in each chart. Ten patients had reflux-associated diagnoses. These were most commonly cerebral palsy, prematurity and Pierre Robin sequence. Other diagnoses were Charcot-Marie-Tooth disease, Velocardiofacial syndrome, Down syndrome and De George's syndrome. Non-reflux medical history was also identified and recorded separately (See Table 2 below). Patients were, in general, referral patients from local family practice clinics, pediatricians, or other pediatric health care professionals. Most patients were referred to ENT for upper airway problems, sinusitis, or recurrent/chronic otitis media that had been refractory to medical therapy as reported by the primary care physician. Symptoms and signs most commonly found in these patients were recorded and tallied. All signs and symptoms were broken down into six major categories: (1) nasal; (2) otologic; (3) respiratory; (4) gastrointestinal; (5) sleep-related; and (6) other. The most common problems fell into one or all of the first 3 categories (See Table 1 below).

Most patients had been treated in the past with medical therapy in the form of antibiotics, steroids, asthma medications and other diagnosis-appropriate therapies. In addition, nine of the patients had been on reflux therapy in the past, most commonly in the form of conservative therapy such as head of bed elevation 30°, avoidance of evening snacks, avoidance of caffeinated beverages as well as cisapride and ranitidine (See Graph 3 below).

The proton pump inhibitor suspension used in this group of patients was Choco-Base suspension of either lansoprazole or omeprazole. The dosing was very uniform, with patients receiving doses of either 10 or 20 mg of omeprazole and 23 mg of lansoprazole. Initially, in April of 1996 when therapy was first instituted 10 mg of omeprazole was used. There were 3 patients in this early phase who were treated initially with 10 mg po qd of omeprazole. All three subsequently were increased to either 20 mg po qd of omeprazole or 23 mg po qd of lansoprazole. All remaining patients were given either the 20 mg omeprazole or the 23 mg lansoprazole treatment qd, except in one case, where 30 mg of lansoprazole was used. Patients were instructed to take their doses once per day, preferably at night in most cases. Suspensions were all filled through the University of Missouri Pharmacy at Green Meadows. This allowed for tracking of usage through refill-data.

Most patients responded favorably to and tolerated the once daily dosing of Choco-Base proton pump inhibitor suspension. Two patients had documented adverse effects associated with the use of the PPI suspension. In one a patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment failure. The other patient had small amounts of bloody stools per mother. This patient never had his stool tested, as his bloody stool promptly resolved upon cessation of therapy, with no further sequellae. The other 23 patients had no documented adverse effects.

Patients were categorized based on review of clinic notes and chart review into general categories: (1) improved; (2) unchanged; (3) failed; and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of PPI therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical findings while on therapy, one complained of worsening symptoms while on therapy, one patient had therapy as prophylaxis for surgery, and two stopped therapy just after its commencement (see graph 4). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which PPI therapy was for purely prophylactic reasons, leaves (17/21) 81% of patients that responded to Choco-Base suspension. This means that 19% (4/21) of patients received no apparent benefit from PPI therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were mild bloody stool that completely resolved upon cessation of therapy.

Discussion.

GERD in the pediatric population is relatively common, affecting almost 50% of newborns. Even though most infants outgrow physiologic reflux, pathologic reflux still affects approximately 5% of all children, throughout childhood. Recently considerable data has pointed to reflux as an etiologic factor in extra-esophageal areas. GERD has been attributed to sinusitis, dental caries, otitis media, asthma, apnea, arousal, pneumonia, bronchitis, and cough, among others. Despite the common nature of reflux, there seems to have been little improvement in therapy for reflux, especially in the non-surgical arena.

The standard of therapy for the treatment of GERD in the pediatric population has become a progression from conservative therapy to a combination of a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, PPI therapy is effective in 90% of those treated for gastroesophageal reflux disease. As a medical alternative to

the H-2 blockers, the proton pump inhibitors have not been studied extensively in the pediatric population. Part of the reason for this lack of data may be related to the absence of a suitable dosage formulation for this very young population, primarily under 2 years of age, that does not swallow capsules or tablets. It would be desirable to have a true liquid formulation (solution or suspension) with good palatability such as is used for oral antibiotics, decongestants, antihistamines, H-2 blockers, cisapride, metoclopramide, etc. The use of lansoprazole granules (removed from the gelatin capule) and sprinkled on applesauce has been approved by the Food and Drug Administration as an alternative method of drug administration in adults but not in children. Published data are lacking on the efficacy of the lansoprazole sprinkle method in children. Omeprazole has been studied for bioequivalence as a sprinkle in adults and appears to produce comparable serum concentrations when compared to the standard capsule. Again no data are available on the omeprazole sprinkle in children. An additional disadvantage of omeprazole is its taste which is quinine-like. Even when suspended in juice, applesauce or the like, the bitter nature of the medicine is easily tasted even if one granule is chewed. For this reason applicant eventually progressed to use lansoprazole in Choco-Base. Pantoprazole and rabeprazole are available as enteric-coated tablets only. Currently, none of the proton pump inhibitors available in the United States are approved for pediatric use. There is some controversy as to what the appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective PPI dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity with the PPI's is not seen even at >50 mg/kg, there appears little risk associated with the higher dosages. Based on observations at the University of Missouri consistent with the findings of this review, applicant established a simple fixed dosage regimen of 10 ml Choco-Base suspension daily. This 10 ml dose provided 20 mg omeprazole and 23 mg lansoprazole.

In the ICU setting, the University of Missouri-Columbia has been using an unflavored PPI suspension given once daily per various tubes (nasogastric, g-tube, jejunal feeding tube, duo tube, etc.) for stress ulcer prophylaxis. It seemed only logical that if this therapy could be made into a palatable form, it would have many ideal drug characteristics for the pediatric population. First, it would be liquid, and therefore could be administered at earlier ages. Second, if made flavorful it could help to reduce noncompliance. Third, it could afford once daily dosing, also helping in reducing noncompliance. In the process, applicant discovered that the dosing could be standardized, which nearly eliminated dosing complexity.

Choco-Base is a product which protects drugs which are acid labile, such as proton pump inhibitors, from acid degradation. The first few pediatric patients with reflux prescribed Choco-Base were sicker patients. They had been on prior therapy and had been diagnosed both by pH probe and endoscopy. In the first few months, applicant treated patients with 10 mg of omeprazole qd (1 mg/kg) and found this to be somewhat ineffective, and quickly increased the dosing to 20 mg (2 mg/kg) of omeprazole. About halfway through the study, applicant began using lansoprazole 23 mg po qd. Applicant's standard therapy was then either 20 mg of omeprazole or 23 mg of lansoprazole once daily. The extra 3 mg of lansoprazole is related only to the fact that the final concentration was 2.25 mg/ml, and applicant desired to keep dosing simple, so he used a 10 ml suspension.

The patients that were treated represented a tertiary care center population, and they were inherently sicker and refractory to medical therapy in the past. The overall 72% success rate is slightly lower than the 90% success rates of PPIs in the adult population, but this can be attributed to the refractory nature of their illness, most having failed prior non-PPI treatment. The population in this study is not indicative of general practice populations.

Conclusion.

PPI therapy is a beneficial therapeutic option in the treatment of reflux related symptoms in the pediatric population. Its once daily dosing and standard dosing scheme combined with a palatable formulation makes it an ideal pharmacologic agent.

TABLE 1

Symptoms	Patient Numbers
Nasal:	35
Sinusitis	7
Congestion	8
Nasal discharge	16
Other	4
Otologic:	26
Otitis Media	17
Otorrhea	9
Respiratory:	34
Cough	10
Wheeze	11
Respiratory Distress:	5
Pneumonia	2
Other	6
Gastrointestinal:	10
Abdominal Pain	1
Reflux/Vomiting	4
Other	4
Sleep Disturbances:	11
Other	2

TABLE 2

Past Medical History	Number of Patients
Reflux Associated:	12
Premature	5
Pierre-Robin	2
Cerebral Palsy	2
Down Syndrome	1
Charcot-Marie-Tooth	1
Velocardiofacial Syndrome	1
Other Medical History	12
Cleft Palate	3
Asthma	3
Autism	2
Seizure Disorder	1
Diabetes Mellitus	1
Subglottic Stenosis	1
Tracheostomy Dependent	1

FORMULATION 1

PART A INGREDIENTS	AMOUNT (mg)
Omeprazole	200
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150

-continued

Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT (ml)**
Distilled Water	100

COMPOUNDING INSTRUCTIONS

Add Part B to Part A to create a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.

FORMULATION 2

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT**
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg

COMPOUNDING INSTRUCTIONS

Mix the constituents of Part B together thoroughly and then add to Part A. This results in a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.

FORMULATION 3

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT**
Distilled Water	100 ml
Omeprazole	200 mg

COMPOUNDING INSTRUCTIONS

This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.

-continued

FORMULATION 4

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT**
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg

COMPOUNDING INSTRUCTIONS

This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.

In all four of the above formulations, lansoprazole or other PPI can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200 mg of omeprazole. Additionally, aspartame can be substituted for sucrose, and the following other ingredients can be employed as carriers, adjuvants and excipients: maltodextrin, vanilla, carrageenan, mono and diglycerides, and lactated monoglycerides. One skilled in the art will appreciate that not all of the ingredients are necessary to create a Choco-Base formulation that is safe and effective.

Omeprazole powder or enteric coated granules can be used in each formulation. If the enteric coated granules are used, the coating is either dissolved by the aqueous diluent or inactivated by trituration in the compounding process.

Applicant additionally analyzed the effects of a lansoprazole Choco-Base formulation on gastric pH using a pH meter (Fisher Scientific) in one adult patient versus lansoprazole alone. The patient was first given a 30 mg oral capsule of Prevacid®, and the patient's gastric pH was measured at 0, 4, 8, 12, and 16 hours post dose. The results are illustrated in FIG. 4.

The Choco-Base product was compounded according to Formulation 1 above, except 300 mg of lansoprazole was used instead of omeprazole. A dose of 30 mg lansoprazole Choco-Base was orally administered at hour 18 post lansoprazole alone. Gastric pH was measured using a pH meter at hours 18, 19, 24, 28, 32, 36, 40, 48, 52, and 56 post lansoprazole alone dose.

FIG. 4 illustrates the lansoprazole/cocoa combination resulted in higher pH_s at hours 19–56 than lansoprazole alone. at hours 4–18. Therefore, the combination of the lansoprazole with chocolate enhanced the pharmacologic activity of the lansoprazole. The results establish that the sodium bicarbonate as well as chocolate flavoring and calcium were all able to stimulate the activation of the proton pumps, perhaps due to the release of gastrin. Proton pump inhibitors work by functionally inhibiting the proton pump and effectively block activated proton pumps

(primarily those inserted into the secretory canalicular membrane) By further administering the proton pump inhibitor with one of these activators or enhancers, there is a synchronization of activation of the proton pump with the absorption and subsequent parietal cell concentrations of the proton pump inhibitor. As illustrated in FIG. 4, this combination produced a much longer pharmacologic effect than when the proton pump inhibitor was administered alone.

EXAMPLE VI

Combination Tablet Delivering Bolus and Time-released Doses of PPI

Tablets were compounded using known methods by forming an inner core of 10 mg omeprazole powder mixed with 750 mg sodium bicarbonate, and an outer core of 10 mg omeprazole enteric-coated granules mixed with known binders and excipients. Upon ingestion of the whole tablet, the tablet dissolves and the inner core is dispersed in the stomach where it is absorbed for immediate therapeutic effect. The enteric-coated granules are later absorbed in the duodenum to provide symptomatic relief later in the dosing cycle. This tablet is particularly useful in patients who experience breakthrough gastritis between conventional doses, such as while sleeping or in the early morning hours.

EXAMPLE VII

Therapeutic Application

Patients were evaluable if they met the following criteria: had two or more risk factors for SRMD (mechanical ventilation, head injury, severe burn, sepsis, multiple, trauma, adult respiratory distress syndrome, major surgery, acute renal failure, multiple operative procedures, coagulotherapy, significant hypotension, acid-base disorder, and hepatic failure), gastric pH of ≦4 prior to study entry, and no concomitant prophylaxis for SRMD.

The omeprazole solution was prepared by mixing 10 ml of 8.4% sodium bicarbonate with the contents of a 20 mg capsule of omeprazole (Merck & Co.. Inc., West Point, Pa.) to yield. a solution having a final omeprazole concentration of 2 mg/ml.

Nasogastric (ng) tubes were placed in the patients and an omeprazole dosage protocol of buffered 40 mg omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$—8.4%) followed by 40 mg of the same buffered omeprazole solution in eight hours, then 20 mg of the same buffered omeprazole solution per day, for five days. After each buffered omeprazole solution administration, nasogastric suction was turned off for thirty minutes.

Eleven patients were evaluable. All patients were mechanically ventilated. Two hours after the initial 40 mg dose of buffered omeprazole solution, all patients had an increase in gastric pH to greater than eight as shown in FIG. 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four when administered 20 mg omeprazole solution. One patient required 40 mg omeprazole solution per day (closed head. injury, five total risk factors for SRMD). Two patients were changed to omeprazole solution after having developed clinically significant upper gastrointestinal bleeding while receiving conventional intravenous H_2-antagonists. Bleeding subsided in both cases after twenty-four hours. Clinically significant upper gastrointestinal bleeding did not occur in the other nine patients. Overall mortality was 27%, mortality attributable to upper gastrointestinal bleeding was 0%. Pneumonia developed in one patient after initiating omeprazole therapy and was present upon the initiation of omeprazole therapy in another patient. The mean length of prophylaxis was five days.

A pharmacoeconomic analysis revealed a difference in the total cost of care for the prophylaxis of SRMD:

ranitidine (Zantac®) continuous infusion intravenously (150 mg/24 hours)×five days $125.50;

cimetidine (Tagamet®) continuous infusion intravenously (900 mg/24 hours)×five days $109.61;

sucralfate one gm slurry four times a day per (ng) tube×five days $73.00; and

buffered omeprazole solution regimen per (ng) tube×five days $65.70.

This example illustrates the efficacy of the buffered omeprazole solution of the present invention based on the increase in gastric pH, safety and cost of the buffered omeprazole solution as a method for SRMD prophylaxis.

EXAMPLE VIII

Effect on pH

Experiments were carried out in order to determine the effect of the omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$—8.4%) administration on the accuracy of subsequent pH measurements through a nasogastric tube.

After preparing a total of 40 mg of buffered omeprazole solution, in the manner of Example VII, doses were administered into the stomach, usually, through a nasogastric (ng) tube. Nasogastric tubes from nine different institutions were gathered for an evaluation. Artificial gastric fluid (gf) was prepared according to the USP. pH recordings were made in triplicate using a Microcomputer Portable pH meter model 6007 (Jenco Electronics Ltd., Taipei, Taiwan).

First, the terminal portion (tp) of the nasogastric tubes was placed into a glass beaker containing the gastric fluid. A 5 ml aliquot of gastric fluid was aspirated through each tube and the pH recorded; this was called the "pre-omeprazole solution/suspension measurement." Second, the terminal portion (tp) of each of the nasogastric tubes was removed from the beaker of gastric fluid and placed into an empty beaker. Twenty (20) mg of omeprazole solution was delivered through each of the nasogastric tubes and flushed with 10 ml of tap water. The terminal portion (tp) of each of the nasogastric tubes was placed back into the gastric fluid. After a one hour incubation, a 5 ml aliquot of gastric fluid was aspirated through each nasogastric tube and the pH recorded; this was called the "after first dose SOS [Simplified Omeprazole Solution] measurement." Third, after an additional hour had passed, the second step was repeated; this was called the "after second dose SOS [Simplified Omeprazole Solution] measurement." In addition to the pre-omeprazole measurement, the pH of the gastric fluid was checked in triplicate after the second and third steps. A change in the pH measurements of +/− 0.3 units was considered significant. The Friedman test was used to compare the results. The Friedman test is a two way analysis of variance which is used when more than two related samples are of interest, as in repeated measurements.

The results of these experiments are outlined in Table 1.

TABLE 1

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
[1] gf Pre SOS	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[2] gf p 1st dose 1.3←check of fg pH	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[3] gf p 2nd Dose 1.3←check of gf pH	1.3	1 3	1.4	1.4	1.4	1.3	1.4	1.3	1.3

SOS pH = 9.0

Table 1 illustrates the results of the pH measurements that were taken during the course of the experiment. These results illustrate that there were no statistically significant latent effects of omeprazole solution administration (per nasogastric tube) on the accuracy of subsequent pH measurements obtained through the same nasogastric tube.

EXAMPLE IX

Efficacy of Buffered Omeprazole Solution in Ventilated Patients

Experiments were performed in order to determine the efficacy, safety, and cost of buffered omeprazole solution in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Patients: Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage.

Interventions: Patients received 20 ml omeprazole solution (prepared as per Example VII and containing 40 mg of omeprazole) initially, followed by a second 20 ml dose six to eight hours later, then 10 ml (20 mg) daily. Omeprazole solution according to the present invention was administered through a nasogastric tube, followed by 5–10 ml of tap water. The nasogastric tube was clamped for one to two hours after each administration.

Measurements and Main Results: The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage and was associated with a five percent decrease in hematocrit. Secondary efficacy measures were gastric pH measured four hours after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the incidence of adverse events and the incidence of pneumonia. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric pH was 7.1 (mean), the mean gastric pH after starting omeprazole was 6.8 (mean) and the lowest pH after starting omeprazole was 5.6 (mean). The incidence of pneumonia was twelve percent. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions: Omeprazole solution prevented clinically significant upper, gastrointestinal bleeding and maintained gastric pH above 5.5 in mechanically ventilated critical care patients without producing toxicity.

Materials and Methods

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population: All adult (>18 years old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated intensive care unit stay of at least forty-eight hours were considered for inclusion in the study. To be included patients also had to have a gastric pH of <4, had to be mechanically ventilated and have one of the following additional risk factors for a minimum of twenty-four hours after initiation of omeprazole suspension: head injury with altered level of consciousness, extensive burns (>20% Body Surface Area), acute renal failure, acid-base disorder, multiple trauma, coagulopathy, multiple operative procedures, coma, hypotension for longer than one hour or sepsis (see Table 2). Sepsis was defined as the presence of invasive. pathogenic organisms or their toxins in blood or tissues resulting in a systematic response that included two or more of the following: temperature greater than 38° C. or less than 36° C., heart rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute (or $_pO_2$ less than 75 mm Hg), and white blood cell count greater than 12,000 or less than 4,000 cells/mm^3 or more than 10 percent bands (Bone, Let's Agree on Terminology: Definitions of Sepsis, Crit. Care Med., 19: 27 (1991)). Patients in whom H_2-antagonist therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count less than 30,000 cells/mm^3) ; were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH above four for forty-eight hours after ICU admission (without, prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having non-stress-related mucosal bleeding. The reason for this exclusion is the confounding effect of non-stress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration: Omeprazole solution was prepared immediately before administration by the patient's nurse using the following instructions: empty the contents of one or two 20 mg omeprazole capsule(s) into an empty 10 ml syringe (with 20 gauge needle in place) from which the plunger has been removed. (Omeprazole delayed-release capsules, Merck & Co., Inc., West Point, Pa.); replace the plunger and uncap the needle; withdraw 10 ml of 8.4% sodium bicarbonate solution or 20 ml if 40 mg given (Abbott Laboratories, North Chicago, Ill.), to create a concentration of 2 mg omeprazole per ml of 8.4% sodium bicarbonate; and

allow the enteric coated pellets of omeprazole to completely breakdown, 30 minutes (agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before administration. The solution was not administered with acidic substances. A high pressure liquid chromatography study was performed that demonstrated that this preparation of simplified omeprazole suspension maintains >90% potency for seven days at room temperature. This preparation remained free of bacterial and fungal contamination for thirty days when stored at room temperature (See Table 5).

The initial dose of omeprazole solution was 40 mg, followed by a second 40 mg dose six to eight hours later, then a 20 mg daily dose administered at 8:00 AM. Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5–10 ml of tap water and clamped for at least one hour. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube was removed and the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures: The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-minute lavage or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, Calif.) positive coffee ground material for four consecutive hours that did not clear with lavage (at least 100 ml) and produced a 5% decrease in hematocrit.

Secondary Outcome Measures: The secondary efficacy measures were gastric pH measured four hours after omeprazole was administered, mean gastric pH after starting omeprazole and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, N.Y.) was used to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of one pH unit. Gastric pH was measured before the initiation of omeprazole solution therapy, immediately before each dose, and every four hours between doses.

Other secondary outcome measures were incidence of adverse events (including drug interactions) and pneumonia. Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Prevention and Control definition of nosocomial pneumonia (Garner et al., 1988). According to these criteria, a patient who has pneumonia is one who has rales or dullness to percussion on physical examination of the chest or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and has at least two of the following present: new purulent sputum or changes in character of the sputum, an organism isolated from blood culture, fever or leukocytosis, or evidence of infection from a protective specimen brush or bronchoalveolar lavage. Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia incidence figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present prior to the start of omeprazole suspension.

Cost of Care Analysis: A pharmacoeconomic evaluation of stress ulcer prophylaxis using omeprazole solution was performed. The evaluation included total drug cost (acquisition and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental confusion), costs associated with clinically significant upper gastrointestinal bleeding. Total drug cost was calculated by adding the average institutional costs of omeprazole 20 mg capsules, 50 ml sodium bicarbonate vials, and 10 ml syringes with needle; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

Statistical Analysis: The paired t-test (two-tailed) was used to compare gastric pH before and after omeprazole solution administration and to compare gastric pH before omeprazole solution administration with the mean and lowest gastric pH value measured after beginning omeprazole.

Results:

Seventy-seven patients met the inclusion and exclusion criteria and received omeprazole solution (See FIG. 2). Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down prior to the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above six as soon as the patient was given a dose of omeprazole solution (in which the enteric coated pellets of omeprazole had been allowed to completely breakdown).

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained above four in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared failures, their pH values were no longer followed.

The ages of the remaining seventy-five patients ranged from eighteen to eighty-seven years; forty-two patients were male and thirty-three were female. All patients were mechanically ventilated during the study. Table 2 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was two to ten, with a mean of 3 (±1) (standard deviation). Five patients enrolled in the study had developed clinically significant bleeding while receiving continuous infusions of ranitidine (150 mg/24 hr) or cimetidine (900 mg/24 hr). In all five cases, the bleeding subsided and the gastric pH rose to above five within thirty-six hours after initiating omeprazole therapy. Three patients were enrolled after having developed two consecutive gastric pH values below three while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH rose to above five within four hours after omeprazole therapy was initiated. Four other patients were enrolled in this study after experiencing confusion (n=2) or thrombocytopenia (n=2) during H_2-antigens therapy. Within thirty-six hours of switching therapy, these adverse events resolved.

Stress-related Mucosal Bleeding and Mortality: None of the sixty-five patients who received buffered omeprazole solution as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant

upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only (Gastroccult-positive) within eighteen hours of starting omeprazole solution; bleeding stopped in all patients within thirty-six hours. The overall mortality rate in this group of critically ill patients was eleven percent. No death was attributable to upper gastrointestinal bleeding or the use of omeprazole solution.

Gastric pH: The mean (±standard deviation) pre-omeprazole gastric pH was 3.5±1.9. Within four hours of omeprazole administration, the gastric pH rose to 7.1±1.1 (See FIG. 3); this difference was significant (p<0.001). The differences between pre-omeprazole gastric pH and the mean and lowest gastric pH measurements during omeprazole administration (6.8±0.6 and 5.6±1.3, respectively) were also statistically significant (p<0.001).

Safety: Omeprazole solution was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have been drug-related thrombocytopenia. However, the platelet count continued to fall after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus was unable to continue on omeprazole. No. clinically. significant drug interactions with omeprazole were noted during the study period. As stated above, metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in omeprazole solution was small (12 mEq/10 ml) and no electrolyte abnormalities were found.

Pneumonia: Pneumonia developed in nine (12%) patients receiving omeprazole solution. Pneumonia was present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic evaluation: The average length of treatment was nine days. The cost of care data are listed in Tables 3 and 4. The costs of drug acquisition, preparation, and delivery for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 3. There were no costs to add from toxicity associated with omeprazole solution. Since two of seventy-five patients required 40 mg of omeprazole solution daily to adequately control gastric pH, the acquisition/preparation cost should reflect this. The additional 20 mg of omeprazole with vehicle adds seven cents per day to the cost of care. Therefore, the daily cost of care for omeprazole solution in the prophylaxis of stress-related mucosal bleeding was $12.60 (See Table 4).

Omeprazole solution is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has been challenged recently. All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage—mechanical ventilation. Previous trials and data from a recently published study show that stress ulcer prophylaxis is of proven benefit in patients at risk and, therefore, it was thought to be unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during omeprazole solution therapy. Gastric pH was maintained above 4 on omeprazole 20 mg/day in seventy-three of seventy-five patients. No adverse events or drug interaction associated with omeprazole were encountered.

TABLE 2

Mech Vent	Major Surgery	Multi-trauma	Head Injury	Hypo-tension	Renal Failure	Sepsis	Multiple Operation	Acid/ Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2

Risk factors present in patients in this study (n = 75)

TABLE 3

		Per day
RANITIDINE (day-9)		
Rantidine	150 mg/24 hr	6.15
Ancillary Product (1)	Piggyback (60%)	0.75
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs × 50%)	14.50
TOTAL far 9 days	→	304.20
RANITIDINE Cost per day	→	33.80
CIMETIDINE (day 1–9)		
Cimetidine	900 mg/24 hr	3.96
Ancillary Product (1)	Piggyback	1.25
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.		
Pump cost	3 minutes ($40/hr)	2.00
TOTAL for 9 days	$29/24 hrs × 50%)	14.50
CIMETIDINE Cost per day	→	288.99
SUCRALFATE (day 1–9)	→	32.11
Sucralfate	1 Gm × 4	2.40
Ancillary Product (1)	syringe	.20
Sterile Prep required	no	
R.N. time ($24/hr)	30 minutes/day (includes pH monitoring)	12.00
TOTAL for 9 days	→	131.40
SUCRALFATE Cost per day	→	14.60

Note: Does not include the cost of failure and/or adverse effect.
Acquisition, preparation and delivery costs of traditional agents.

EXAMPLE X

Bacteriostatic and Fungistatic Effects of Omeprazole Solution

The antimicrobial or bacteriostatic effects of the omeprazole solution were analyzed by applicant. An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made according to the present invention was stored at room temperature for four weeks and then was analyzed for fungal and bacterial growth. Following four weeks of storage at room temperature, no bacterial or fungal growth was detected.

An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made in accordance with the present invention was stored at room temperature for twelve weeks and then was analyzed for fungal and bacterial growth. After twelve weeks of incubation at room temperature, no fungal or bacterial growth was detected.

The results of these experiments illustrate the bacteriostatic and fungistatic characteristics of the omeprazole solution of the present invention.

EXAMPLE XI

Bioequivalency Study

Healthy male and female study participants over the age of 18 will be randomized to receive omeprazole in the following forms:

(a) 20 mg of a liquid formulation of approximately 20 mg. omeprazole in 4.8.mEq sodium bicarbonate qs to 10 ml with water;

(b) 20 mg of a liquid formulation of approximately 2 mg omeprazole per 1 ml of 8.4% sodium bicarbonate.

(c) Prilosec® (omeprazole) 20 mg capsule;

(d) Capsule prepared by inserting the contents of an omeprazole 20 mg capsule into a #4 empty gelatin capsule (Lilly) uniformly dispersed in 240 mg of sodium bicarbonate powder USP to form an inner capsule. The inner capsule is then inserted into a #00 empty gelatin capsule (Lilly) together with a homogeneous mixture of 600 mg sodium bicarbonate USP and110 mg pregelatinized starch NF.

Methodology

After appropriate screening and consent, healthy volunteers will be randomized to receive one of the following four regimens as randomly assigned by Latin Square. Each subject will be crossed to each regimen according to the randomization sequence until all subjects have received all four regimens (with one week separating each regimen).

Regimen A (20 mg omeprazole in 4.8 mEq sodium bicarbonate in 10 ml volume); Regimen B (20 mg omeprazole in 10 ml 8.4% sodium bicarbonate in 10 ml volume); Regimen C (an intact 20 mg omeprazole capsule); Regimen D (Capsule in capsule formulation, see above). For each dose/week, subjects will have an i.v. saline lock placed for blood sampling. For each regimen, blood samples will be taken over 24 hours a total of 16 times (with the last two specimens obtained 12 hours and 24 hours after drug administration).

Patient Eligibility

Four healthy females and four healthy males will be consented for the study.

Inclusion Criteria

Signed informed consent.

Exclusion Criteria

1. Currently taking H_2-receptor antagonist, antacid, or sucralfate.
2. Recent (within 7 days) therapy with lansoprazole, omeprazole, or other proton pump inhibitor.
3. Recent (within 7 days) therapy with warfarin.
4. History of variceal bleeding.
5. History of peptic ulcer disease or currently active G.I. bleed.
6. History of vagotomy or pyloroplasty.
7. Patient has received an investigational drug within 30 days.
8. Treatment with ketoconazole or itraconazole.
9. Patient has an allergy to omeprazole.

Pharmocokinetic Evaluation and Statistical Analysis

Blood samples will be centrifuged within 2 hours of collection and the plasma will then separated and frozen at −10° C. (or lower) until assayed. Pharmacokinetic variables will include: time to peak concentration, mean peak concentration, AUC (0-t) and (0-infinity). Analysis of variance will be used to detect statistical difference. Bioavailability will be assessed by the 90% confidence interval of the two one-sided tests on the natural logarithm of AUC.

HPLC Analysis

Omeprazole and internal standard (H168/24) will be used. Omeprazole and internal standard will be measured by modification of the procedure described by Amantea and Narang. (Amantea Mass., Narang PK. Improved Procedure for Quantification of Omeprazole and Metabolites Using Reversed-Phased High Performance Liquid Chromotography. J. Chromatography 426; 216–222. 1988). Briefly, 20 ul of omeprazole 2 mg/ml $NaHCO_3$ or Choco-Base omeprazole suspension and 190 ul of the internal standard are vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml of dichloroethane, 5 ml of hexane, and 980 ul of sterile water. After the sample is centrifuged, the organic layer is extracted and dried over a nitrogen stream. Each pellet is reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul is injected onto a C_{18} 5 U column equilibrated with the same mobile phase at 1.1 ml/min. Under these conditions, omeprazole is eluted at approximately 5 minutes, and the internal standard at approximately 7.5 minutes. The standard curve is linear over the concentration range 0–3 mg/ml (in previous work with SOS), and the between-day coefficient of variation has been <8% at all concentrations. The typical mean R2 for the standard curve has been 0.98 in prior work with SOS (omeprazole 2 mg/ml $NaHCO_3$ 8.4%).

Applicant expects that the above experiments will demonstrate there is more rapid absorption of formulations (a), (b) and (d) as compared to the enteric coated granules of formulation (c). Additionally, applicant expects that although there will be a difference in the rates of absorption among forms (a) through (d), the extent of absorption (as measured by the area under the curve (AUC)) should be similar among the formulations (a) through (d).

EXAMPLE XII

Intraveneous PPI in Combination With Oral Parietal Cell Activator

Sixteen (16) normal, healthy male and female study subjects over the age of 18 will be randomized to receive pantoprazole as follows:

(a) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of sodium bicarbonate 8.4%; and

(b) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of water.

The subjects will receive a single dose of (a) or (b) above, and will be crossed-over to (a) and (b) in random fashion. Serum concentrations of pantoprazole versus time after administration data will be collected, as well as. gastric pH control as measured with an indwelling pH probe.

Further, similar studies are contemplated wherein chocolate or other parietal cell activator is substituted for the parietal cell activator sodium bicarbonate, and other PPIs are substituted for pantoprazole. The parietal cell activator can be administered either within about 5 minutes before, during or within about 5 minutes after the IV dose of PPI.

Applicant expects that these studies will demonstrate that significantly less IV PPI is required to achieve therapeutic effect when it is given in combination with an oral parietal cell activator.

Additionally, administration kits of IV PPI and oral parietal cell activator can be packaged in many various forms for ease of administration and to optimize packing and shipping the product. Such kits can be in unit dose or multiple dose form.

EXAMPLE XIII

Twelve (12) Month Stability of Omeprazole Solution

A solution was prepared by mixing 8.4% sodium bicarbonate with omeprazole to produce a final concentration of 2 mg/ml to determine the stability of omeprazole solution after 12 months. The resultant preparation was stored in clear glass at room temperature, refrigerated and frozen. Samples were drawn after thorough agitation from the stored preparations at the prescribed times. The samples were then stored at 70° C. Frozen samples remained frozen until they were analyzed. When the collection process was completed, the samples were shipped to a laboratory overnight on dry ice for analysis. Samples were agitated for 30 seconds and sample aliquots were analyzed by HPLC in triplicate according to well known methods. Omeprazole and the internal standard were measured by a modification of the procedure described by Amantea and Narang. Amantea Mass., Narang PK, Improved Procedure For Quantitation Of Omeprazole And Metabolites Using Reverse-Phased High-Performance Liquid Chromatography, J. Chromatography, 426: 216–222 (1988). Twenty (20) ul of the omeprazole 2 mg/ml $NaHCO_3$ solution and 100 ul of the internal standard solution were vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml dichloroethane, 5 ml hexane, and 980 ul of sterile water. The sample was centrifuged and the organic layer was extracted and dried over a nitrogen stream. Each pellet was reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul were injected onto a C185u column equilibrated with the same mobile phase at 1.1 ml/min. Omeprazole was eluted at ~5 min, and the internal standard at ~7.5 min. The standard curve was linear over the concentrated range 0–3 mg/ml, and between-day coefficient of variation was <8% at all concentrations. Mean R2 for the standard curve was 0.980.

The 12 month sample showed stability at greater than 90% of the original concentration of 2 mg/ml. (i.e., 1.88 mg/ml, 1.94 mg/ml, 1.92 mg/ml).

Throughout this application various publications and patents are referenced by citation and number. The disclosure of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation. Obviously, many modifications, equivalents, and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described.

I claim:

1. A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and

(b) at least one buffering agent selected from the group consisting of sodium bicarbonate, potassium bicarbonate, a calcium salt, and a magnesium salt, in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor; wherein the dosage form is selected from the group consisting of suspension tablet, chewable tablet, effervescent powder, and effervescent tablet.

2. The composition as recited in claim 1, wherein the proton pump inhibitor is omeprazole.

3. The composition as recited in claim 1, wherein the proton pump inhibitor is lansoprazole.

4. The composition as recited in claim 1, wherein the proton pump inhibitor is rabeprazole.

5. The composition as recited in claim 1, wherein the proton pump inhibitor is esomeprazole.

6. The composition as recited in claim 1, wherein the proton pump inhibitor is pantoprazole.

7. The composition as recited in claim 1, wherein the proton pump inhibitor is pariprazole.

8. The composition as recited in claim 1, wherein the proton pump inhibitor is leminoprazole.

9. The composition as recited in claim 1, further comprising at least one flavoring agent.

10. The composition as recited in claim 1, further comprising an anti-foaming agent.

11. The composition as recited in claim 1, wherein the dosage form is a suspension tablet.

12. The composition as recited in claim 1, wherein the dosage form is a chewable tablet.

13. The composition as recited in claim 12, further comprising aspartame.

14. The composition as recited in claim 1, wherein the dosage form is an effervescent powder.

15. The composition as recited in claim 1, wherein the dosage form is an effervescent tablet.

16. The composition as recited in claim 1, wherein the buffering agent is at least about 1680 mg sodium bicarbonate.

17. The composition as recited in claim 1, wherein the buffering agent is about 1000 mg to about 1680 mg sodium bicarbonate.

18. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 11 with an aqueous medium.

19. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 12 with an aqueous medium.

20. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 14 with an aqueous medium.

21. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 15 with an aqueous medium.

22. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form of claim 1 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

23. The method as recited in claim 22, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

24. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject a solid pharmaceutical composition in a dosage form that is not enteric-coated; wherein the composition comprises active ingredients consisting essentially of:

(a) a therapeutically effective amount of approximately 5 mg to approximately 300 mg of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole,

esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent in an amount of approximately 1.0 mEq to approximately 150 mEq selected from the group consisting of a bicarbonate salt of a group IA metal, a calcium salt, and a magnesium salt, wherein the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.

25. The method of claim 24, wherein the calcium salt is selected from the group consisting of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium bicarbonate, calcium gluconate, and other calcium salts.

26. The method of claim 24, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg.

27. The method of claim 24, wherein the sodium bicarbonate is in an amount of at least about 1680 mg.

28. The method of claim 24, wherein the calcium salt is calcium carbonate present in an amount from about 250 mg to about 1000 mg.

29. The method of claim 24, wherein the calcium salt is calcium carbonate present in an amount from about 500 mg to about 1000 mg.

30. The method of claim 24, wherein the calcium salt is calcium carbonate present in an amount of at least about 1000 mg.

31. The method of claim 24, wherein the buffering agent is in an amount of at least 10 mEq.

32. The method of claim 24, wherein the buffering agent is in an amount from about 10 mEq to about 70 mEq.

33. The method of claim 24, wherein the buffering agent is in an amount from about 20 mEq to about 40 mEq.

34. The method of claim 24, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

35. The method of claim 24, wherein the proton pump inhibitor is omeprazole.

36. The method of claim 35, wherein the omeprazole is present in an amount of about 10 mg.

37. The method of claim 35, wherein the omeprazole is present in an amount of about 20 mg.

38. The method of claim 35, wherein the omeprazole is present in an amount of about 40 mg.

39. The method of claim 35, wherein the omeprazole is present in an amount of about 60 mg.

40. The method of claim 35, wherein the omeprazole is present in an amount of about 80 mg.

41. The method of claim 35, wherein the omeprazole is present in an amount of about 100 mg.

42. The method of claim 24, wherein the proton pump inhibitor is lansoprazole.

43. The method of claim 42, wherein the lansoprazole is present in an amount of about 15 mg.

44. The method of claim 42, wherein the lansoprazole is present in an amount of about 30 mg.

45. The method of claim 42, wherein the lansoprazole is present in an amount of about 45 mg.

46. The method of claim 42, wherein the lansoprazole is present in an amount of about 60 mg.

47. The method of claim 42, wherein the lansoprazole is present in an amount of about 90 mg.

48. The method of claim 42, wherein the lansoprazole is present in an amount of about 100 mg.

49. The method of claim 24, wherein the proton pump inhibitor is micronized.

50. The method of claim 24, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

51. The method of claim 24, wherein the subject is a human.

52. The method of claim 24, wherein the dosage form further comprises a flavoring agent.

53. The method of claim 52, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

54. The method of claim 24, wherein the composition is provided as a separate component of a kit.

55. The method of claim 24, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

56. The method of claim 24, wherein the dosage form is administered once or twice a day.

57. A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent selected from the group consisting of sodium bicarbonate, and calcium carbonate, in an amount more than about 40 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

58. The composition as recited in claim 57, wherein the buffering agent is sodium bicarbonate.

59. The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount from about 400 mg to about 4000 mg.

60. The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

61. The composition as recited in claim 57, wherein the buffering agent is calcium carbonate.

62. The composition as recited in claim 57, wherein the calcium carbonate is in an amount from about 400 mg to about 4000 mg.

63. The composition as recited in claim 61, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

64. The composition as recited in claim 61, wherein the calcium carbonate is in an amount of at least about 800 mg.

65. The composition as recited in claim 57, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

66. The composition as recited in claim 57, wherein the proton pump inhibitor is omeprazole.

67. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 10 mg.

68. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 20 mg.

69. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 40 mg.

70. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 60 mg.

71. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 80 mg.

72. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 100 mg.

73. The composition as recited in claim 57, wherein the proton pump inhibitor is lansoprazole.

74. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 15 mg.

75. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 30 mg.

76. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 45 mg.

77. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 60 mg.

78. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 90 mg.

79. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 100 mg.

80. The composition as recited in claim 57, wherein the proton pump inhibitor is micronized.

81. The composition as recited in claim 57, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

82. The composition as recited in claim 57, further comprising a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

83. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 50 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

84. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 60 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

85. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 70 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

86. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 80 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

87. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 90 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

88. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 100 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

89. The composition as recited in claim 57, wherein the composition is provided as a separate component of a kit.

90. A method of producing a liquid pharmaceutical composition comprising: combining the dosage form of claim 57 with an aqueous medium.

91. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form as recited in claim 57 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

92. The method as recited in claim 91, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

93. The method as recited in claim 91, wherein the composition is administered once or twice a day.

94. A method for administering a liquid pharmaceutical composition to a subject, comprising: combining the pharmaceutical composition as recited in claim 57 with an aqueous medium to form a suspension, and orally administering the suspension to the subject in a single dose without administering an additional buffering agent.

95. The composition as recited in claim 1, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

96. The composition as recited in claim 95, wherein the proton pump inhibitor is omeprazole.

97. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 10 mg.

98. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 20 mg.

99. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 40 mg.

100. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 60 mg.

101. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 80 mg.

102. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 100 mg.

103. The composition as recited in claim 95, wherein the proton pump inhibitor is lansoprazole.

104. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 15 mg.

105. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 30 mg.

106. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 45 mg.

107. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 60 mg.

108. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 90 mg.

109. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 100 mg.

110. The composition as recited in claim 1, wherein the proton pump inhibitor is micronized.

111. The composition as recited in claim 9, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

112. The composition as recited in claim 1, wherein the composition is provided as a separate component of a kit.

113. The composition of claim 1, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

114. The composition of claim 1, wherein the buffering agent comprises at least one of magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, or magnesium silicate.

115. The composition of claim 1, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, or other calcium salts.

116. The composition of claim 1, further comprising a disintegrant, flow aid, lubricant, adjuvant excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

117. The method of claim 24, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

118. The composition of claim 57, further comprising a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

* * * * *

tab 3

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Patent Number: 6489346 **Application Number:** 09481207

	4th Year	8th Year	12th Year
Opening	12/05/2005	12/03/2009	12/03/2013
Surcharge	06/06/2006	06/04/2010	06/04/2014
Closing	12/04/2006	12/03/2010	12/03/2014

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tab 4

Attorney Docket No. 01723326 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent Application of: Jeffrey Owen Phillips	)	
Serial No.: 09/481,207	)	Examiner: Fan, J.
Filed: January 11, 2000	)	Group Art Unit: 1625
For: Novel Substituted Benzimidazole Dosage Forms and Method of Using Same	)	

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
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Tim Hubalik
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(signature of person mailing paper or fee)

TERMINAL DISCLAIMER UNDER 37 § CFR 1.321

Assistant Commissioner of Patents
Washington, D. C. 20231

Sir:

I, Joseph A, Mahoney, represent that I am the attorney of record for this application, that The Curators of the University of Missouri, a nonprofit organization, owns all of the right, title and interest in the above-identified application Serial No. 09/481,207; which is a continuation-in-part of United States Serial No. 09/183,422, which is a continuation-in-part of United States Serial No. 08/680,376, filed July 15, 1996, now U.S. Patent No. 5,840,737. Your petitioner, Joseph A. Mahoney, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the above-identified application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. § 154 to 156 and 173 of United States Patent No. 5,840,737, and hereby agrees that any patent so granted on the above-identified applications shall be enforceable only for and during such period that the legal title to such patent shall be the same as the legal title of United States Patent No. 5,840,737, this agreement to run with any patent granted on the above-identified application and to be binding upon the grantee, its successors and assigns.

In making the above disclaimer petitioner does not disclaim any terminal part of any patent granted on the above-identified application that would extend to the expiration date of the full or extended statutory term as defined in 35 U.S.C. § 154 to 156 and 173 of United States Patent No. 5,840,737, or later: expires for failure to pay a maintenance fee, is held

unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. § 1.321, has all claims canceled by a reexamination certificate, is reissued, or is otherwise terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

Further, the petitioner does not disclaim any right to extend the term of any patent issued for the above-identified application under 35 U.S.C. § 156 from the date of expiration for such patent as is imposed by this terminal disclaimer.

The evidentiary documents accompanying or referred to in the Instant Terminal Disclaimer have been reviewed by the undersigned and it is certified that to the best of my knowledge and belief, title is in the assignee.

Submitted simultaneously herewith is check in the amount of $55.00 for the fee under 37 CFR § 1.20(d) for filing a statutory disclaimer under 37 CFR § 1.321 by a small entity as defined in 37 CFR § 1.27(a). If there are any additional fees due in connection with the filing of this response, please charge these additional fees (or credit any overpayment) associated with this communication to our Deposit Account No. 13-0019.

Respectfully submitted,

Dated: November 19, 2001

By: Joseph A. Mahoney

Joseph A. Mahoney
Registration No. 38,956
Mayer, Brown & Platt
P.O. Box 2828
190 S. LaSalle Street
Chicago, IL 60690-2828
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tab 5

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,489,346

DATED : December 3, 2002

INVENTOR(S) : Phillips, J.O.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 36
Line 51, after Table 3, please insert Tables 4 and 5 as follows:

--TABLE 4

The average length of treatment was 9 days. Cost of care was calculated from these days.

		Per Day	Total
OMEPRAZOLE (day 1)			
Product acquisition cost	40 mg load x 2 5.66/dose)	11.32	11.32
Ancillary product	materials for solution preparation	0.41	0.41
Ancillary product	syringe w/needle	0.20	0.40
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
OMEPRAZOLE (days 2-9)			
Product acquisition cost	20 mg per day	2.80	22.65
Ancillary product	materials for solution preparation	0.41	0.82
Ancillary product	syringe w/needle	0.20	1.60
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	18 minutes/day (includes pH monitoring)	8.40	57.60
2/75 patient require 40 mg simplified omeprazole solution per day (days 2-9)			0.63
No additional cost for adverse effects or for failure			
TOTAL	113.43		
Simplified Omeprazole Solution cost per day	12.60		

Pharmacoeconomic evaluation of omeprazole cost of care

MAILING ADDRESS OF SENDER:

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PATENT NO. 6,489,346

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,489,346
DATED : December 3, 2002
INVENTOR(S) : Phillips, J.O.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

TABLE 5

Time	Control	1 hour	24 hour	2 day	7 day	14 day
Conc (mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

Stability of Simplified Omeprazole Solution at room temperature (25° C.). Values are the mean of three samples.--

Column 37
Line 14, delete “bicarbonate.” and insert --bicarbonate;--, therefor.
Line 63, after “plasma will then”, insert --be--, therefor.

Column 38
Line 11, delete “Choco-Base” and insert --Choco-BaseTM--, therefor.
Line 12, after “suspension and”, delete “190” and insert --100--, therefor.

Column 39
Line 22, after “suspension and”, delete “190” and insert --100--, therefor.

MAILING ADDRESS OF SENDER:

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PATENT NO. 6,489,346

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CERTIFICATE OF CORRECTION

PATENT NO. : 6,489,346

DATED : December 3, 2002

INVENTOR(S) : Phillips, J.O.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1
After "an enantiomer, isomer," insert --derivative,--, therefor.

Column 2
Line 17, delete "cimetidine" and insert --Cimetidine--, therefor.
Line 19, delete "39" and insert --30--, therefor.
Line 41, delete "64" and insert --84--, therefor.
Line 48, delete "Antacids" and insert --antacids--, therefor.
Line 63, delete "64" and insert --84--, therefor.

Column 9
Line 42, delete "Brunton" and insert --Goodman AG, et al.--, therefor.
Lines 43-44, delete "In Goodman A G, et al." and insert --in--, therefor.

Column 13
Line 31, delete "inhibitor" and insert --inhibitors--, therefor.

Column 20
Lines 32-33, after "Dextrose 10 mg" insert a new line as follows: --Calcium Hydroxide 10 mg--

Column 22
Lines 51-52, delete "Choco-Base," and insert --Choco-BaseTM"--, therefor.
Line 56, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.

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PATENT NO. 6,489,346

Joseph A. Mahoney
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CERTIFICATE OF CORRECTION

PATENT NO. : 6,489,346

DATED : December 3, 2002

INVENTOR(S) : Phillips, J.O.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

<u>Column 23</u>
Line 29, after "males and 6" insert --were--, therefor.

<u>Column 24</u>
Line 21, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.

<u>Column 28</u>
Line 39, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.
Line 46, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.
Line 55, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.

<u>Column 36</u>
Line 30, after "TOTAL", delete --far-- and insert --for--, therefor.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Phillips, J.O.	) ATTORNEY DOCKET:	01723326
PATENT NO.:	6,489,346	) GROUP ART UNIT:	1625
FILED:	January 11, 2000	) EXAMINER:	Fan, J.
TITLE:	Substituted Benzimidazole Dosage Forms and Method of Using Same		
		CUSTOMER NO.:	26565

DECLARATION OF DAVID C. YEOMANS, Ph.D. IN SUPPORT OF APPLICATION FOR PATENT TERM EXTENSION

I, David C. Yeomans, Ph.D., declare:

1. I am the Director of the Stanford Pain Research Center and on the Faculty of the Department of Anesthesia at Stanford University School of Medicine in Stanford, California. I make the statements in this Declaration from my own personal knowledge, and if required, could and would testify competently to the facts contained herein.

Background and Experience

2. I have a Doctoral degree in Neuroscience from University of Florida and a Bachelor of Arts degree in Psychology from Dartmouth College. I also did a Post-doctoral fellowship in Pharmacology at the University of Illinois. A true and correct copy of my Curriculum Vitae is attached as Exhibit A.

3. In my role as Director of the Stanford Pain Research Center, I provide guidance and coordination of pharmacologic research relevant to anesthesia and pain across Stanford University. This work includes the development and use of novel models to help understand how pain in different body systems works, and how best to therapeutically

manipulate these mechanisms. This work further includes extensive analysis of the pharmacological interactions among various drugs and drug combinations.

4. As part of my investigations relating to drug interactions, I discovered an important synergy in the analgesic effects of N-type calcium channel blockers and morphine as more fully described in my publication titled "Combined Effects of N-type Calcium Channel Blockers And Morphine On A-delta vs. C Fiber Mediated Nociception," a copy of which is attached as Exhibit B. This particular discovery has provided me with an understanding of the methodologies and analysis necessary to distinguish pharmacologic synergies from those drug interactions that are not synergistic.

5. A subset of the general field of pain research is the specific research relating to gastric acidity induced pain. In animal models, I have routinely conducted research relating to the pharmacologic inhibition of pain induced by injection of noxious chemicals into the gastric cavity. This experience has provided me with substantial working knowledge of pain and pain inhibition with gastric tissue.

Undertaking

6. Due to my extensive pharmacology background, and more specifically to my experience with pharmacological interactions, I have been asked to determine whether a synergistic effect and/or other pharmacological interaction results from the combination of the proton pump inhibitor, Omeprazole[1], and an antacid Buffer[2].

[1] "Omeprazole" as used in this Declaration is 40 mg of uncoated or "naked" omeprazole (*i.e.*, not enteric coated).
[2] "Buffer" as used in this Declaration is 20 mEq of sodium bicarbonate or 30 mEq of a 1:1 mixture of sodium bicarbonate and calcium carbonate. I refer to Omeprazole and the Buffer individually in this Declaration as a

Summary of Conclusions

7. For the reasons provided in this Declaration, I have concluded that the combination of these two Compounds produces a pharmacological interaction. Furthermore, I have concluded that this interaction is synergistic.

8. With regard to my conclusion that a synergistic effect exists for the combination of the Compounds, I specifically conclude that the effect of the combination of the two Compounds was greater than the sum of their predicted individual acid reducing effects. In fact, for the Compounds tested, the acid reducing effects for the combination was supra-additive when compared to the sum of the effects of each Compound administered alone (see Figure 1 below). Thus, when the Omeprazole was co-administered with the Buffer to adult volunteers, the resultant data demonstrated a 500% (5-fold) increase in the acid reducing effect of the combination over the sum of the effects of Omeprazole the Buffer alone.

9. With regard to my conclusion that a pharmacological interaction exists for the combination of the Compounds, I specifically conclude that the effect of the combination of the Compounds described in the paragraph above is an example of a pharmacological interaction for two reasons. First, the administration of the Buffer influences acid reducing effects of administration of the Omeprazole. Second, for the reasons provided above that show a synergistic effect between the two Compounds, I also conclude that a pharmacological interaction is inherently present if there is a finding of synergy.

"Compound" and collectively as "Compounds." It is also my understanding that the combination of the Omeprazole and the Buffer comprise the product known as Zegerid™.

Definitions

10. Before explaining the analysis I performed in reaching my conclusions above, I first provide generally accepted definitions for synergy and pharmacological interaction, as are well known by pharmacologists such as myself.

11. Synergy has a very specific meaning in pharmacology. The phenomenon of *synergy* is understood to mean that if the *measured* effects of a combination of two drugs are greater than that *predicted* by the sum of the effects of the individual drugs, the combination is considered to be *synergistic*. Synergy may be explained by reference to a number of variables that are analyzed using three steps: a measured effect step, a predicted effect step, and a statistical analysis of the results of these two steps.

12. For the measured effect step, three variables must be experimentally measured for two drugs, A and B: (i) measured effect of drug A (Variable A); (ii) measured effect of drug B (Variable B); and (iii) measured effect of the combination of drug A and drug B (CM).

13. For the predicted effect step, A is added to B resulting in a predicted (additive) combined effect (CP).

14. For the statistical analysis step, CM is compared to CP to determine whether CM is significantly greater than CP. If the statistical analysis shows that CM is statistically significantly greater than CP, then synergy exists by the combination.

15. By way of example, if a dose of drug X produces variable A of 2, and a dose of drug Y produces a variable B of 3, then we would expect that combining these two doses

of the two drugs would produce a CP of 5 (2 + 3 = 5). Thus, the pharmacologic interaction between the two drugs would be considered *additive.* On the other hand, if the measured effect (CM) of these two doses of the two drugs produces an effect that is statistically significantly greater than 5, say a CM of 20, then the combination of these two drugs can be considered to form a pharmacologic *synergy*.

16. There are several mathematical models for examining data for synergy, but all have similar underlying principles. *See*, *e.g.*, Tallarida, Drug Synergism and Dose-Effect Data Analysis, Boca Raton: CRC Press, 2000. Specifically, these models look to see if the experimental results of combinations of two drugs are significantly greater than the predicted result of that same combination. Procedurally, synergy may be determined by conducting certain statistical analyses of experimental data using standard computer statistical applications as described further below.

17. Pharmacological interaction is a more broadly defined term than synergy. Pharmacological interaction describes a condition where the effect of one drug on a body is influenced by the co-administration of another drug on the same body. Some examples of the types of pharmacological interaction include sub-additive, additive and supra-additive (synergistic) effects of the drugs where the two or more drugs have a similar (i.e. overt) general effect on the body.

18. With these general definitions in mind, I now explain the analyses performed in reaching the conclusions above.

Background Information Related To Analysis Performed

19. I conducted this analysis in my office at Stanford University School of Medicine in Stanford, California.

20. I began my analysis by reviewing experimental data, protocols from pilot studies and other studies ("Pre-NDA Information") collected as part of an NDA application to the Food and Drug Administration for the product Zegerid™. This Pre-NDA Information had already been collected during development of this product and the tests were not performed solely for my analysis below.

21. In addition to the Pre-NDA Information, I also independently reviewed scientific literature relevant to the scope of this analysis.

22. After reviewing the Pre-NDA Information and the relevant scientific literature, I focused my analysis on experimental protocols and data from the Pre-NDA Information, as well as the following particular items:

a. U.S. Patent Nos. 6,699,885, 6,645,988, 6,489,346, and 5,840,737 attached as Exhibit C.

b. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest,* 2000; 117:260-267 attached as Exhibit D.

c. Pilbrant A, Cederberg C. Development of an oral formulation of omeprazole. *Scand J Gastroenterol Suppl.* 1985;108:113-20 attached as Exhibit E.

d. Kaunitz JD, Akiba Y. Duodenal intracellular bicarbonate and the 'CF paradox'. *J. Pancreas*, 2001 Jul;2(4 Suppl):268-73 attached as Exhibit F.

e. Thomson AB, Pinchbeck B, Kirdeikis J, Kirdeikis P, Zuk L, Brunet MK, Jurima-Romet M, Murray PE, Evaluation of antacid tablets and liquid in fasting and fed men and women. *Clin Ther.* 1988;10(2):158-68 attached as Exhibit G.

f. Fordtran JS, Morawski SG, Richardson CT. In vivo and in vitro evaluation of liquid antacids. *N Engl J Med.* 1973 May 3;288(18):923-8 attached as Exhibit H.

23. From these items, the following experimental parameters are noted as relevant factors for the analysis.

24. First, in all the experiments that I relied upon, healthy human volunteers were used. At least seven (7) subjects were tested for each drug/group. My experience in pharmacologic testing indicates that this sample size is adequate for the analysis performed.

25. Second, the Compounds were administered orally.

26. Third, all experimental data that I relied upon was from unfed (fasted or premeal) subjects.

27. Fourth, during the course of the experiments that I relied upon, gastric pH was measured at various time points prior to and after administration of the Compounds. Gastric pH is an appropriate endpoint to evaluate acid neutralizing capacity of acid reducing formulations. In some cases, data had been converted to integrated gastric acidity (IGA) in mmol.hr/L (also an appropriate endpoint), prior to my receiving the data. In those cases

where data was sent in raw pH format, I converted this data to IGA to allow direct comparison. To do this, I used the same formula as used throughout the Pre-NDA Information that I relied upon. The formula is as follows:

$$\text{Acid Concentration (mM)} = 1000 \times 10^{-pH}$$

$$\text{IGA} = (\text{Acid Concentration at time "}t_0\text{"} + \text{Acid Concentration at time "}t_1\text{"}) / 2 \times (t_0 - t_1)$$

Thus, IGA was used to indicate gastric acidity at different time points.

Analysis

28. With these parameters in mind, I conducted the analysis described below. The object of the analysis was to statistically compare (i) the *measured* acid reducing effect (CM as defined above) of a combination of Omeprazole and the Buffer to (ii) the *predicted* acid reducing effect (CP as defined above) of the same combination based on the sum of the effects of the two Compounds administered alone (A + B).

29. In order to assess, statistically, whether the interaction observed between the two Compounds met the requirements of phamacologic synergy, data had to be re-expressed as "difference scores." That is, in order to be able to directly compare acidity effects produced by different Compounds, the effect of the Compounds needed to be converted to a value normalized by subtracting a "control value," in this case the last pre-drug acidity value. Thus, for any given time point, these difference scores give a true assessment of acid reducing efficacy of a treatment. Difference scores were therefore created from measured acidity after administering each of the two Compounds alone or administering the combination of the Compounds together. The measured difference scores for the combination of Compounds are referred to as the "Measured Combination Values".

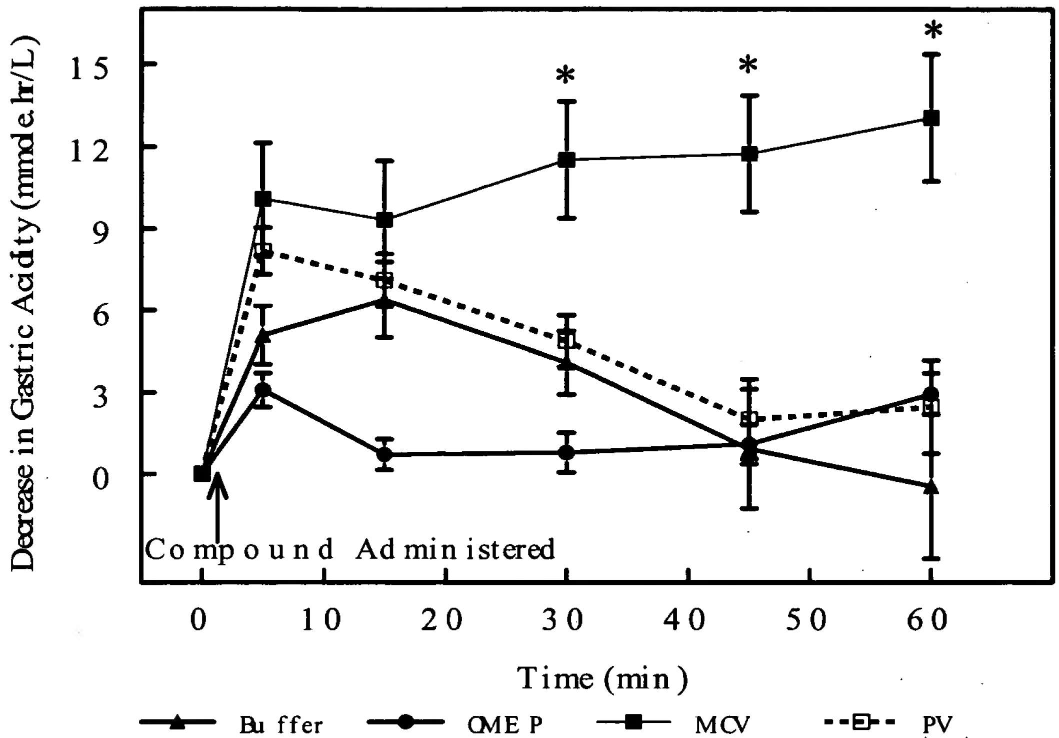
30. Furthermore, by combining measured difference scores obtained from data measured after separate administration of either Compound, I calculated the *predicted* effect of a combination of the two by simply adding the two sets of difference scores ("Predicted Values").

31. The Predicted Values then were statistically compared to the Measured Combination Values.

32. Statistical analysis was performed to determine if there was an overall significant difference between Predicted Values of the Omeprazole/Buffer combination and the Measured Combination Values using a two-way Analysis of Variance with "predicted vs. measured" and "time after dose" as dependent variables. For this analysis, significance was set at $p < 0.05$; in other words, there is a less than a 5% chance that the results of the analysis occurred randomly. If the Analysis of Variance indicated that the Measured Combination Values were significantly greater than the Predicted Values, the combination of the Compounds were considered synergistic. Follow up analyses were made using a Bonferroni's test (a well known statistical test) to look for significant differences at particular time points after administration of the Compounds.

Results

Figure 1. Difference Scores for Actual and Predicted Gastric Acidity



33. Figure 1 shows the difference scores for: (i) the Measured Values[3] of the two Compounds alone; and (ii) the Measured Combination Values (filled squares; MCV) of the combined Compounds. From Figure 1, it is clear that the acid reducing effects of the Buffer alone (filled triangles; Buffer), though robust, are short-lived; the effect of Omeprazole alone (filled circles; OMEP) is fairly minimal; while the effects of the combination of the Compounds (Measured Combination Values) are large, and long lasting.

34. Also in Figure 1, I show the Predicted Values (open squares with broken line; PV) resulting from the simple addition of the Buffer alone value and the Omeprazole alone value (the Measured Values). In examining this Figure, it is clear from its appearance that overall, the actual acid reducing effects of the co-administration of Omeprazole and Buffer

[3] Difference scores for the individual Compounds.

produced substantially greater IGA difference scores than was predicted by the efficacy of the individual Compounds.

35. The impression of a greater than Predicted Value of the combination of Omeprazole and Buffer was confirmed by statistical analysis. The analysis of variance demonstrated an overall significant difference between the Predicted Values and the Measured Combination Values of the two Compounds with a significance level of $p < 0.05$.

36. Furthermore, when individual time point data were analyzed, the actual IGA difference score mean was statistically significantly greater at three later time points (30, 45, and 60 min after drug administration), with individual p values of < 0.05, < 0.001, and < 0.001, respectively. This means that, for example, there is less than a 1 in 1,000 chance that the differences seen at 60 minutes occurred randomly, rather than by synergy. Thus, this difference between the Predicted Values and Measured Combination Values provides clear, strong statistical evidence of *synergy*.

37. It is also worth noting that the trend of higher Measured Combination Values than Predicted Values holds for the two earliest time points, although these differences did not meet the test of statistical significance. In Figure 1, statistically significantly different individual means are denoted by asterisks (*).

Conclusions

38. The results of this analysis clearly demonstrate that both the Buffer and Omeprazole are capable of producing acid reducing effects on gastric contents. When administered alone, however, the Buffer has a robust, but short lived acid reducing effect,

and the Omeprazole produces a minimal acid reducing effect, probably due to its instability in acidic solution.

39. Overall, the combination of the Omeprazole and Buffer demonstrated unpredicted supra-additivity on stomach acidity when compared to the Predicted Values of the two Compounds in combination. Examination of individual means at different time points indicates that this difference is not as significant at early time points, probably due to the fact that the Buffer has a very robust acid reducing effect, which brings the stomach to near neutral levels during these early time points. However, at later time points, the robust synergy becomes clearly evident. In fact, within 60 minutes after administering the two Compounds together, the acid reducing effect was ***5 fold*** greater than that which would be predicted based on the individual effects of the Compounds.

40. In my opinion, therefore, the supra-additivity demonstrated for the combination of Omeprazole and Buffer provides clear evidence of a synergy. Likewise, for these same reasons, I find that the combination of Omeprazole and Buffer provides clear evidence of a pharmacological interaction.

41. It should be noted that for the study from which the Measured Combination Values (filled squares in Figure 1) were derived, 20 mEq of buffering agent was used, whereas in the Buffer alone study (filled triangles in Figure 1) 30 mEq of Buffer was used. It is even more surprising, therefore, that such a large difference in gastric acidity is observed between the Measured Combination Values and the Predicted Values. I would expect that, had the formulation used in the measured combination study contained 30 mEq of Buffer, an even greater difference in gastric acidity would be observed between the Measured

Combination Values and the Buffer alone values, thereby providing even stronger evidence of synergy.

42. Although I analyzed data relating to 40 mg Omeprazole and the Buffer amounts described (*i.e.*, 20 mEq and 30 mEq), all of my conclusions relating to the synergy and pharmacological interaction are equally applicable to a formulation such as Zegerid™ which comprises, *inter alia*, 20 mg Omeprazole and 20 mEq of sodium bicarbonate.

43. The statements made herein are made of my own personal knowledge and are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize any patent term extension which may be granted.

44. Executed this 12 day of August, 2004, in Palo Alto, California.

David C. Yeomans, Ph.D.

Date: August 12, 2004

tab A

CURRICULUM VITAE

Current Date: August 9, 2004

David C. Yeomans, PhD

A. ACADEMIC HISTORY

- Dartmouth College, Hanover, New Hampshire: AB, 1979
- University of Florida, Gainesville, Florida (Charles Vierck, Adv.): PhD, 1989
- University of Illinois, Chicago, Illinois: Post-doctoral fellowship (Herbert Proudfit, Adv.): 1989-1992

B. EMPLOYMENT HISTORY

- Research Associate/Postdoctoral Fellow, Dept. of Pharmacology, University of Illinois at Chicago College of Medicine 2/89-9/92.
- Research Assistant Professor, Dept. of Pharmacology, University of Illinois at Chicago College of Medicine 10/92-8/96.
- Assistant Professor, Depts. of Anatomy and Cell Biology, Anesthesiology, and Pharmacology, University of Illinois at Chicago College of Medicine 9/96-8/00.
- Associate Professor, Department of Anesthesia and Director of Stanford Pain and Analgesia Research Center, Stanford University School of Medicine 9/00 – present.

C. CURRENT AND PENDING FEDERAL FUNDING

- RO1 research grant "Analgesic Effects of Adrenal Chromaffin Cell Transplants" from **National Institute on Drug Abuse** - start date 04/03 - 5yr; Co-Principal Investigator.
- R21 (CEBRA*) research grant "In Vivo Genetic Manipulation of Neuronal Excitability" from **National Institute on Drug Abuse** - start date 04/03 - 2yr; Principal Investigator.
- RO1 research Grant "Cannabanoid Modulation of Hyperalgesia" from **National Institute on Drug Abuse** – start date 02/00 – 5yr, Collaborator.
- R21 (CEBRA*) research grant "Recombinant Herpes Injection into Trigeminal Ganglia" from **National Institute on Drug Abuse** - start date 10/03 - 2yr; Principal Investigator.
- R21 research grant "Differential Activation of Thermonociceptors by Infrared Diode Laser " from **National Institute of Neurological Disease and Stroke** – start date 10/04 – 2yr; Principal Investigator – pending.
- RO1 research grant: "In Vivo Genetic Manipulation of Neuronal Excitability" from **National Institute on Drug Abuse** - start date 12/04 - 5yr; Principal Investigator - pending.
- RO1 research grant: "Genetic Manipulation of Opioids in Orofacial Pain" **from National Institute of Dental and Craniofacial Research** - start date 4/05 - 5yr; Principal Investigator - pending.

* CEBRA = Cutting Edge Basic Research Award

D. PUBLIC AND PROFESSIONAL SERVICE

National Grant Review Committees:

- NIH IRG - ZRG1 IFCN- 7
- NIH IRG CEBRA Program
- NSF IBN
- Spinal Cord Research Foundation
- Veterans Administration

Journals:
Reviewer: Brain Research; Journal of Neurological Research; Neuroscience; Anesthesiology; Pain; Journal of Pain, Gene Therapy, Journal of Pharmacology and Experimental Therapeutics
Guest Editor: Journal of Neurological Research, Seminars in Pain Medicine

University Service:
Stanford Award Committee; Stanford Neuroscience Institute Executive Committee; Theme Chair; Stanford Neuroscience Institute; Vice Chair, Stanford Institutional Animal Care and Use Committee; Grant Reviewer, Zafforoni Fund for Addiction Research at Stanford; Avram Goldstein Endowed Chair Search Committee.

Community Education/Service:
Lecture: "Pain and Analgesia" at local high schools; Lecture/Demonstrations on the brain for 5th graders; Judge for the National Student Research Forum, 1999

Public Education/Popular Media:

- **Society for Neuroscience**, "Purification of chromaffin cells allows xenotransplantation without immunosuppression" - Invited Press Release. "Stimulus-dependent Analgesia after Application of a Transgenic Herpes Virus Encoding Human Proenkephalin to Primate Skin" - Invited Press Release.
- **UIC and Stanford** Public Relations office press release, 3/1999: "Researcher Reports Gene Therapy Can Control Pain." Consequent interviews with: BBC; AM Canada (television news show); Pittsburgh Gazette; Boston Globe; Reuters; Biotechnology News; Folha de S. Paulo (Brazilian Newspaper); The Scientist; ScienceNow; HealthScout; Science News (in Science); Die Welt (*The World* - German Newspaper); SAT1 - German national news television program.
- **National Institutes on Drug Abuse:** Director's Annual Report to the President of the United States; inclusion in *NIDA Notes*
- **Discovery Channel** Three part documentary series on pain - consultant and interviews on basic pain mechanisms and novel approaches to treatment.

E. INDUSTRY

- **PainCeptor:** Consultant and SAB member.
- **Neurolana:** SAB member.
- **Scios:** Consultant and Contractor
- **Stoelting,** Consultant and Co-Investigator
- **Aberdaire Ventures:** Consultant
- **Piper-Jaffrey Ventures** - Consultant
- **Abbott Laboratories:** Consultant and Contractor
- **Elan Pharmaceuticals:** Consultant and SAB member.
- **Lasmed:** Executive and SA Boards member

F. PATENTS GRANTED AND PENDING:

- Methods and compositions for treating back pain
- PKC Isoform-specific Antagonists for Relief of Pain in Infants, Children and Adults
- Methods and Compositions for Evaluating Cell Function in Sensory Neurons
- Methods for Evaluating the Activity of Candidate Analgesic Agents
- Portable Laser And Process For Producing Controlled Pain

G. POST-DEGREE HONORS AND AWARDS AND SOCIETY MEMBERSHIPS

Society for Neuroscience; International Association for the Study of Pain; American Pain Society; American Society of Anesthesiologists; American Society for Neural Transplantation and Repair; College on Problems of Drug Dependency; International Brain Research Organization; American Society of Regional Anesthesia

2002 Pfizer Professor of Pain Medicine

H. BIBLIOGRAPHY

Peer-Reviewed Journal Articles

1. Cooper, B. Y. Vierck, C. J., Jr., and Yeomans, D. C. Selective reduction of second pain sensations by systemic morphine in humans. *Pain*, 24 (1986) 93-116.

2. Yeomans, D, C. and Proudfit, H. K. Projections of substance P-immunoreactive neurons located in the ventrolateral medulla to the A7 noradrenergic nucleus demonstrated using retrograde tracing combined with immunocytochemistry. *Brain Research*, 532 (1990) 329-332.

3. Clark, F. M., Yeomans, D. C. and Proudfit, H. K. The noradrenergic innervation of the spinal cord: differences between two substrains of Sprague-Dawley rats using retrograde tracers combined with immunocytochemistry. *Neuroscience Letters*, 125 (1991) 155-158.

4. Yeomans, D. C., Clark, F. M., Paice, J. A. and Proudfit, H. K. Antinociception induced by electrical stimulation of spinally-projecting noradrenergic neurons in the A7 catecholamine cell group of the rat. *Pain*, 48 (1992) 449-461.

5. Yeomans, D. C. and Proudfit, H. K. Antinociception induced by microinjection of substance P into the A7 catecholamine cell group in the rat. *Neuroscience*, 49 (1992) 681-691.

6. West, W. L., Yeomans, D. C., and Proudfit, H. K., The function of noradrenergic neurons in mediating antinociception induced by electrical stimulation of the locus coeruleous in two different sources of Sprague-Dawley rats. *Brain Research*, 626 (1993) 127-135.

7. Borg, C., Chang, C. T. L., Yeomans, D. C., Dieter, J. P., Komiotis, D., Anderson, E. G., and LeBreton, G. C. Application of anti-peptide antibodies and a new anti-receptor antibody for a single step purification of human platelet, rat brain, and rabbit aorta TXA_2/PGH_2 receptors. *Journal of Biological Chemistry,* 269 (1994) 6109-6116.

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9. Yeomans, D. C., Cooper, B. Y., and Vierck, C. J., Jr. Comparisons of dose-dependent effects of systemic morphine on flexion reflex components and operant avoidance responses of awake non-human primates. *Brain Research*, 670 (1995) 297-302.

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11. Yeomans, D. C. Pirec, V., and Proudfit, H. K. Nociceptive Responses to High or Low Rates of Noxious Cutaneous Heating Are Mediated by Different Nociceptors in the Rat: Behavioral Evidence. *Pain*, 68 (1996) 133-140.

12. Yeomans, D. C. and Proudfit, H. K. Nociceptive Responses to High or Low Rates of Noxious Cutaneous Heating Are Mediated by Different Nociceptors in the Rat: Electrophysiological Evidence. *Pain*, 68 (1996) 141-150.

13. Zacharaiou, V., Goldstein, B., and Yeomans, D. C. Differential release of Substance P in rat spinal cord dorsal horn by different rates of noxious radiant heating of the hindpaw. *Brain Research*, 752 (1997) 143-150.

14. Lu, Y., Pirec, V., and Yeomans, D. C., Differential antinociceptive effects of spinal opioids on foot withdrawal responses evoked by C fiber or Aδ nociceptor activation. *British Journal of Pharmacology*, 121 (1997) 1210-1216.

15. Wilson, S. P., Yeomans, D. C., Bender, M. A., Lu, Y., and Glorioso, J. Antihyperalgisic effects of delivery of enkephalins to mouse nociceptive neurons by a herpes virus encoding proenkephalin, *PNAS*, 96 (1999) 3211-3216.

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18. Wilson S.P., Yeomans D.C. Genetic therapy for pain management. *Curr. Rev Pain*, 4 (2000) 445-50.

19. Agner, C., Yeomans, D.C., Dujovny, M. The neurochemical basis for the applications of the greater omentum in neurosurgery. *Neurol. Res.*, 23 (2001) 7-15.

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22. Balyasnikova, I.V.,Yeomans, D.C., McDonald, T. B., Miletich, D. T. and Danilov, S. G. Antibody-Mediated Lung Endothelium Targeting : *In Vivo* Model in Primates. *Gene Therapy* 9 (2002) 282-90.

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32. Sweitzer, S.M., Medicherla, S.M., Protter, A, Peters, M. C., and Yeomans, D.C. Involvement of p38α MAPK in capsaicin-induced hyperalgesia, *Pain*, in press.

33. Lu, Y., Pappas, G.D., Laurito, C.E., Jing, R., and Yeomans, D.C. Porcine Chromaffin Cells Isolation, Culture, and Transplant for Antinociceptive Effects. *Neurological Res.*; in press.

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35. Tzabazis, A., Klyukinov, M., Manering, N. A., Nemenov' M.I., Shafer, S. L., and Yeomans, D. C. Differential activation of trigeminal C or Aδ nociceptors by infrared diode laser in rats: behavioral evidence. *Pain*, submitted.

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Book Chapters:

1. Vierck, C. J., Jr., Cooper, B. Y., Cohen, R. H., Yeomans, D. C., and Franzén, O. Effects of systemic morphine on monkeys and man: Generalized suppression of behavior and preferential inhibition of pain elicited by unmyelinated nociceptors. In C. von Euler, O. Franzén, U. Lindblom, and D. Ottoson, eds. Somatosensory Mechanisms. Vol. 41, MacMillan Press, London, 1984, pp. 309-321.

2. Vierck, C. J., Jr., Greenspan, J. D., Ritz, L. A., and Yeomans, D. C. The spinal pathways contributing to the ascending conduction and the descending modulation of pain sensations and reactions. In T. L. Yaksh, ed. Spinal Afferent Processing. Plenum Press, New York, 1986, pp. 275-329.

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9. Yeomans, D. C. and Wilson, S. P., Gene Therapy for Pain. In J. Mogil, ed., The Genetics of Pain IASP Press, Seattle, 2004.

10. Tzabazis, A. and Yeomans, D. C. Opioid Modulation of Nociceptive Afferents *in vivo*. In R. F. Schmidt and W. D. Willis, eds. Encyclopedic Reference of Pain, Springer-Verlag, in press.

Abstracts (recent selected):

Sweitzer, S. W., Keifits, V, Jones, T., Mochly-Rosen, D., Kendig, J. J. and Yeomans, D. C. Developmental Regulation Of Formalin-Induced Nociception By Protein Kinase C Epsilon And Gamma 10*th World Congress on Pain*, 2002.

Jones, T. L., Sweitzer, S. M., M-Margeta, M., Peters, M., Wilson, S. P., and Yeomans, D. C. Cutaneous Administration Of Recombinant Herpes Vectors Encoding Gaba-B Antisense Attenuates Intersegmental Hypoalgesia Induced By Aδ Nociceptor Activation 10*th World Congress on Pain*, 2002.

Yeomans, D. C., Saitoh, Y., and Mannes, A. Gene Therapy for Pain: Different Approaches toward a Common Goal. 10*th World Congress on Pain*, 2002.

Yeomans, D. C., Peters, M.C., Gilly, W. F., Levinson, S. R., and Wilson, S. P. Patch-Recording of Identified Herpes Vector-Transfected Primary Afferents. *Soc. for Neurosci. Abstr.*, 29 (2003).

Lu, Y. McNearney, T.A., Wilson, S.P.; Yeomans, D.C. and Westlund, K.N. Enkephalin-Encoding Herpes Simplex Virus-1 Increases Enkephalin Expression In The Ipsilateral Spinal Cord Reducing Hyperalgesia In A Cfa-Induced Monoarthritis Model *Soc. for Neurosci. Abstr.*, 30 (2004).

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Yeomans, D.C., Levinson, S. R., Peters, M.C., Tzabazis, A. Z., Gilly, W. F., Wilson, S. P. and Angelotti, T. Decrease In Inflammatory Hyperalgesia By Herpes Vector-Mediated Knock-Down Of Nav1.7 Sodium Channels In Primary Afferents. *Soc. for Neurosci. Abstr.*, 30 (2004).

Tzabazis, A. Z., Lee, J., and Yeomans, D. C. Long-lasting orofacial antinociception after trigeminal injection of enkephalin-encoding recombinant Herpes simplex virus (HSV) *Soc. for Neurosci. Abstr.*, 30 (2004).

Invited Presentations (selected):

American Pain Society Annual Meeting, New Orleans, Louisiana, 1997. "The Use of Reflexes in Animal Pain Testing" Dinner Symposia on Animal Pain Testing - Invited Participant.

International Neuroplasticity Society Annual Meeting, St. Lucia, 1998. "Spinal Cord Plasticity and Pain" - Invited Symposia Organizer.

University of California at San Francisco, San Francisco, California, 1999. "Gene Therapy for Pain" - Invited Speaker.

Roche Bioscience, Palo Alto, California 1999. "Gene Therapy for Pain" - Invited Speaker.

Freidrich Alexander University, Erlangen, Germany, 1999. "Viral Delivery of Antisense for Calcitonin Gene Related Peptide Produces Antihyperalgesia" - Invited Speaker.

Spring Pain Conference, Grand Cayman, BWI, 2000. "Herpes Viruses as Vectors for Analgesic Antisense" - Invited Speaker.

Merck Bioscience, San Diego, CA, 2000. "Herpes Antisense Vectors for Selective Knock-down of Primary Afferent Proteins." – Invited Speaker.

Deltagen, Inc., Menlo Park, CA, 2001. "Herpes Vectors as Scientific Tools for Pain Research." – Invited Speaker.

Freidrich Alexander University, Erlangen, Germany, 2001. "Intersegmental Interaction Between Different Nociceptor Types" - Invited Speaker.

Annual Society for Neuroscience Meeting, San Diego, CA (2001). "Herpes Simplex Vectors for Gene Therapy for Pain". – Invited participant in NIH sponsored satellite symposium.

Elan Pharmaceuticals, South San Francisco, CA. (2002) "Use of Herpes Vectors as Tools for Understanding Nociceptor Biology". – Invited Speaker.

American Pain Society, Baltimore, MD (2002). "Gene Therapy for Pain using Herpes Vectors" – Invited Symposium Speaker.

10th World Congress on Pain, San Diego, CA (2002). "Use of Herpes Viruses to Alter Pain Mechanisms" – presented as part of symposium "Gene Therapy for Pain: different approaches toward a common goal", which I organized.

Wake Forest University, Greensboro, NC (2002) "Use of Recombinant Viral Vectors to Affect Pain" – Invited Speaker.

University of Illinois, Chicago, IL (2003) "Gene Therapy for Pain" Dinner symposium associated with *Pfizer Visiting Professor of Pain Medicine Award.*

Stanford University, Stanford, CA (2003) "Herpes Vectors for Evaluation of Molecules involved in Pain." – Stanford Brain Research Institute Retreat Invited Speaker.

University of California at San Francisco (2003) "Herpes Vectors for Analgesia Research" – Invited Speaker.

Rinat Neuroscience, Palo Alto, CA (2003) "Herpes Virus Mediated Gene Transfer to Nociceptors" – Invited Speaker.

Stanford University, Stanford, CA (2004) "Pain Therapy in the 21st Century" Invited Participant in public event, " Breakthroughs in Neurological Disorders."

Avocel, Inc. Palo Alto, CA (2004) "Targets for Gene Therapy for Pain" – Invited Speaker.

Spring Pain Conference, Grand Cayman, BWI (2004) "Differential Activation of Nociceptive Afferents" –Invited Symposium.

tab B

The Combined Effects of N-type Calcium Channel Blockers and Morphine on Aδ Versus C Fiber Mediated Nociception

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Departments of *Psychiatry, †Anesthesiology, and ‡Anatomy and Cell Biology, University of Illinois at Chicago College of Medicine, Chicago, Illinois

Intrathecal μ opiates produce analgesia presynaptically by inhibiting calcium ion influx and postsynaptically by increasing potassium flux. Mu receptors are expressed on presynaptic terminals of unmyelinated (C), but not myelinated (Aδ) nociceptors. Thus, μ-opioids such as morphine may act presynaptically to inhibit C, but not Aδ, neurotransmission, and postsynaptically on dorsal horn cells that receive input from Aδ and/or C fiber nociceptors. N-type calcium ion channel blockers, such as ω-conotoxin GVIA (ω-CTX), produce analgesia by impeding flux of calcium ions into Aδ and C fiber nociceptor terminals. Thus, morphine and ω-CTX attenuated C fiber nociception additively, possibly indicating the same presynaptic site of action. Conversely, morphine and ω- CTX were supraadditively analgesic on an Aδ test, indicating that these agents probably have different sites of action. We conclude that although intrathecal application of either morphine or ω-CTX attenuates both Aδ and C fiber mediated nociception in rats, the combined effects are quite different for the two fiber types. Specifically, although coadministration of morphine with ω-CTX produces an additive, apparently presynaptic antinociception for C fiber-mediated responses, the combination produces a clearly supraadditive, and likely synergistic effect on Aδ mediated nociception, probably by acting at pre and postsynaptic sites, respectively.

(Anesth Analg 2001;92:239–43)

Most pain is initiated by activation of specialized primary afferents termed "nociceptors." These fall into two main classes, thinly myelinated Aδ fibers and unmyelinated C fibers (1). These two classes of nociceptors have clearly differentiable anatomical distributions, physiologies, and pharmacologies (2). Aδ and C fiber nociceptors also produce qualitatively discriminable sensations when activated. Thus, concomitant activation of Aδ and C nociceptors produces a double pain; the first, sharp, piercing pain being mediated by Aδ activation, and the second, burning pain is mediated by C fiber activity (3). Thus, different types or qualities of pain may be associated with the predominance of activity of one or the other type of nociceptor.

Postsurgical pain is an example of a clinical condition in which distinct sensations might be ascribed to either C or Aδ activity. A surgical wound likely activates both types of afferents (4). However, in the recovery room, it is likely that pain is dominated by C fiber activity. This is because Aδ afferents rapidly accommodate (decrease or cease firing) with a constant stimulus (such as a wound), whereas C fibers do not, but rather continue firing (4). If however, the wound site is restimulated by movement, for example by coughing, change of dressing, or ambulation, Aδ fibers would be reactivated. Unfortunately, this movement is important in facilitating postsurgical recovery. Thus, C and Aδ nociceptors appear to be involved in different aspects of postsurgical pain and these differences have different implications for recovery from surgical trauma.

C fiber-mediated pain responds well to μ-opioids, whereas Aδ-mediated pain and nociception are much less responsive (2,5–7). Consistent with this is the fact that tonic postsurgical pain is generally well controlled by opiates, whereas wound movement pain requires substantially larger (and more dangerous) doses (8). Thus, it would be useful to attenuate Aδ mediated pain by means other than μ-opioids alone.

Receptors specific for μ-opioids are localized both presynaptically on primary afferent terminals as well as on dendrites and cell bodies of dorsal horn neurons (9). Thus, the analgesia produced by spinal application of μ-opioids occurs by two means: presynaptic inhibition of neurotransmitter release from primary afferent terminals, and postsynaptic inhibition of secondary cells in the dorsal horn (10). The first mechanism,

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which appears to be limited to C fiber nociceptor terminals (11), is mediated by a decrease in inward Ca^{++} conductance (10). The second mechanism occurs by enhancement of postsynaptic K^+ conductance (10), and occurs at secondary dorsal horn cells that receive input from both Aδ and C nociceptors (12). Thus, μ-opioids act by two mechanisms to inhibit C fiber-mediated pain, and one mechanism to inhibit Aδ-mediated pain. These findings probably explain the substantially greater apparent potency (2) and differences in dose-response line slope (11) for C fiber vs Aδ mediated nociception and pain.

The mechanistic differences in μ-opioid analgesic effects also point to potential differences in susceptibility of Aδ and C fiber-mediated nociception to combinational effects of μ-opioids with Ca^{++} channel blockers. N-type Ca^{++} channels appear to be involved in conveying nociceptive messages into the central from the peripheral nervous system (13). Consistent with this, N-type Ca^{++} channels are highly concentrated in central terminals of primary afferents (14), and N-type Ca^{++} channel blockers have analgesic effects alone (15,16) and in combination with μ-opioids (17–19). Large doses of N-type Ca^{++} channel blockers given alone are generally necessary to produce significant analgesia, which may produce side effects (15), indicating a relatively small therapeutic index. In combination with opioids, however, Ca^{++} channel blockers appear to produce stronger analgesia (19). The nature of this interaction is not clear, however, in that some investigators have described additive effects (17) whereas others have reported pharmacologic synergy (18,19). These differences may be a result of undescribed differences in the types of afferent activity producing the pain or nociceptive responses under investigation. The purpose of this study was to investigate the effects of an N-type Ca^{++} channel blocker in a model of nociception in which the contribution of C and Aδ nociceptors has been defined (2,20) as well as to describe potential interactions between the μ-opioid morphine and an N-type Ca^{++} channel blocker.

Methods

Sprague-Dawley rats (300–400 g) were lightly anesthetized with urethane (750 mg/kg). Intrathecal (IT) catheters were implanted as previously described (11). All drugs were injected IT in a volume of 10 μL saline, followed by 10 μL of saline to ensure that the entire drug dose reached the site of action, the lumbar enlargement. Catheter placement was confirmed at the end of each experiment by histological examination. Blood pressure was continuously monitored by using a specially made blood pressure cuff and transducer (Stoelting) to ensure that the antinociceptive effects of either drug were not contaminated by blood pressure changes.

Responses evoked by thermal activation of Aδ and C nociceptors were separately assessed as previously described (21). Briefly, latencies were measured to foot withdrawals elicited by the output of a projection bulb focused on the dorsolateral or dorsomedial surfaces of either hind paw. The bulb intensity was set so as to increase the surface skin temperature either at a high (6.5°C/s) or low (0.9°C/s) average rate. The low rate evokes responses mediated by C fiber activation, whereas the high rate evokes responses mediated by that activation of Aδ nociceptors (20). The response latencies of the four skin surfaces were averaged and expressed as the foot withdrawal latency (FWL). To minimize tissue damage by prolonged heating in the absence of foot responses, trials were terminated after cutoff latencies of 20 s for the low and 6 s for the high heating rate trials. In addition, there was a 3-min interval between high and low rate testing to allow the skin to return to baseline temperatures (21).

Baseline FWLs were determined. Thereafter, animals were IT administered saline vehicle, the N-type Ca^{2+} channel blocker ω-conotoxin GVIA (ω-CTX) (22,23), morphine, or a combination of morphine and ω-CTX. The ω-CTX was administered in one of four doses (0.1, 0.5, 0.7, or 1.0 nmoles). Preliminary experiments indicated that larger doses of ω-CTX produced potentially contaminating nonspecific motor effects (24). Morphine was given in doses of 0.5, 1.0, 1.5, 3.0, or 5.0 nmoles. For those animals receiving a combination of drugs, ω-CTX (0.5 nmoles) was injected 20 min before the injection of morphine (1.0 nmole). Drug effects on response latencies were determined immediately after the drug injection, and at 15 min intervals for 2 h. Eight animals were used for each dose.

In all behavioral experiments, a one-way analysis of variance was used to assess the effects of each drug, and a least-squares means test was used for *post hoc* comparisons of test dose vs saline controls. Because Aδ mediated and C fiber mediated responses occur at different latencies, but similar skin temperatures (21), we standardized our measures by converting latencies to calculated subsurface skin temperatures at response according to the following formula (11):

$$T_r = L_r \times H + T_b$$

where T_r = subsurface skin temperature at response, L_r = response latency, H = heating rate (2.5°C/s for Aδ stimulation; 0.6°C/s for C stimulation), and T_b = average baseline temperature = (in this case) 35°C.

Dose-response curves were constructed where possible and 50% effective dose values (ED_{50} values) were calculated by the method of Tallarida and Murray (25). Statistical comparisons were made, where appropriate, between drug effects on responses to high or

low-rate skin heating. All experimental procedures were in accordance with the guidelines of the Committee for Research and Ethical Issues of the International Association for the Study of Pain, and were reviewed and approved by the University of Illinois Animal Care Committee.

Results

IT applications of either the N-type Ca^{2+} channel blocker ω-CTX or morphine produced antinociception on the foot withdrawal test. The administration of ω -CTX (0.1, 0.5, 0.7, and 1.0 nmoles) produced significant, dose-dependent increases in FWLs in rats for at least 2 h after injection (Figure 1). There were, however, differences in the time-course of effects for high vs low rate heating, in that the high rate effects were more slow in developing (Figure 1). Both morphine and ω-CTX produced dose-dependent antinociceptive effects for both high and low rate responses (Figure 2), with ED_{50} values for high and low heating rates calculated as 2.10 nmoles (confidence level [CL] = 1.71–2.45) and 0.64 nmoles (CL = 0.57–0.71), respectively for morphine and 0.293 nmoles (CL = 0.199–0.356) and 0.282 nmoles (CL = 0.114–1.465), respectively for ω-CTX. Thus, although morphine was somewhat more potent in attenuating C vs Aδ mediated nociception, ω-CTX demonstrated a similar potency for both response types. No significant cardiovascular effects of either drug were observed.

In addition to examining the antinociceptive properties of ω-CTX injected alone, an additional purpose of this study was to investigate whether morphine doses needed to produce adequate analgesia could be reduced by concomitant application of N-type Ca^{2+} channel blockers. To this end, we have studied the antinociceptive effects of a combination of a small dose of ω-CTX with a small dose of morphine. IT injection of 1.0 nmole of morphine produces a weak antinociceptive effect on responses evoked by low, but not high, rate heating. Similarly, 0.5 nmoles of ω-CTX alone produces only a weak antinociceptive effect on responses to low or high rate skin heating. When coadministered with 1.0 nmole of morphine however, 0.5 nmoles of ω-CTX significantly (ANOVA; $P < 0.05$) and supraadditively potentiated morphine's antinociceptive effect on responses to high rate skin heating (Figure 3). For low rate responses however, the combination of the two drugs was additive.

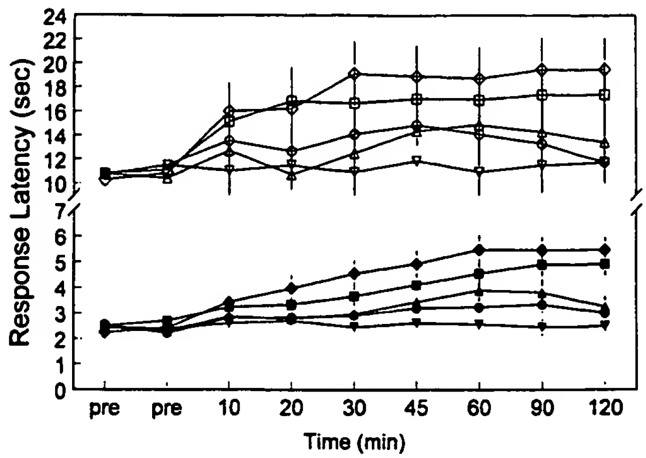

Figure 1. Time course of behavioral antinociceptive effects of different doses of intrathecal ω-conotoxin GVIA (ω-CTX) on responses to high rate (Aδ; filled symbols) or low rate (C; open symbols) skin heating. Downward pointing triangles = mean (across animals) foot withdrawal latency after the administration of vehicle; Circles = response after 0.1 nmole; Squares = response after 0.5 nmole; Upward pointing triangles = response after 0.7 nmole; Diamonds = response after 1.0 nmole ω-CTX.

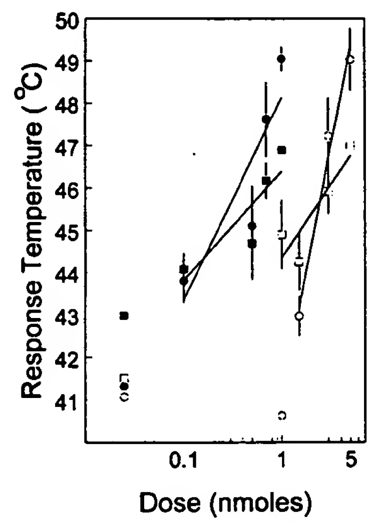

Figure 2. Dose response lines for antinociceptive effects of intrathecal application of ω-conotoxin GVIA (ω-CTX) (filled symbols) and morphine (open symbols), for A-δ responses (circles; R = 0.89 for ω-CTX, R = 0.94 for morphine) and C fiber (squares; R = 0.88 for ω-CTX, R = 0.91 for morphine) mediated responses.

Discussion

The antinociceptive effects of IT application of N-type Ca^{++} channel blockers have been previously described. Calcium ion flux through N-type channels is critical in evoking neurotransmitter release from presynaptic terminals of nociceptors (23,24). Thus, blocking these channels necessarily attenuates nociceptive transmission. Because the same mechanism applies to both Aδ and C fiber nociceptors (as well as non-nociceptive afferents), application of ω-CTX should, and does, attenuate both Aδ and C fiber thermonociception with similar potency.

IT application of μ-opioids produce antinociception by two means: an increase in K^+ conductance and consequent hyperpolarization of postsynaptic dorsal horn neurons and a presynaptic reduction in Ca^{++}

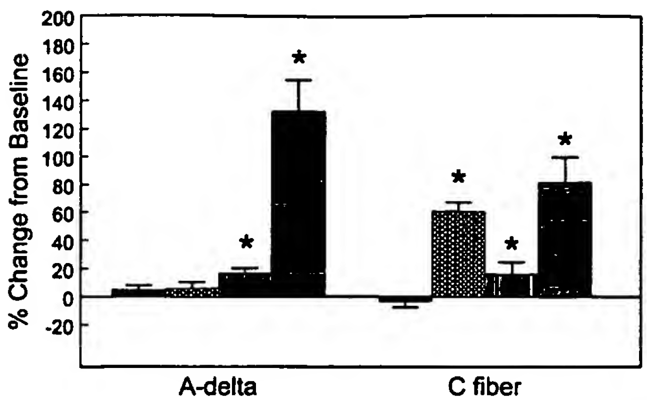

Figure 3. Antinociceptive effects of intrathecal application of vehicle (solid black bars), 1.0 nmole morphine alone (cross-hatched bars), 0.5 nmole ω-conotoxin GVIA (ω-CTX) alone (vertical stripes), or coadministration of 1.0 nmole morphine with 0.5 nmole ω-CTX (horizontal lines). Asterisks indictate response latencies that are significantly elevated from baseline (analysis of variance, $P < 0.05$).

entry through N-type channels (10). Thus, the underlying means by which both ω-CTX and morphine's binding to presynaptic opiate receptors act to produce antinociception is essentially the same. Because it is likely that C but not Aδ thermonociceptors possess μ-opioid receptors on presynaptic terminals, the effect of morphine on C thermonociception occurs by two means, whereas effects on Aδ nociception occurs only by increases in postsynaptic K^+ conductance. As the presynaptic effects on Ca^{++} conductance likely occur at smaller opioid concentrations than the postsynaptic effects (11), the uniformity of mechanism with ω-CTX accounts for the apparently additive antinociceptive effect that was observed for C fiber-mediated responses when a combination of these two drugs was given. However, it is likely that Aδ nociceptors do not possess presynaptic μ-opioid receptors. Morphine's effects on Aδ mediated nociception are likely to occur postsynaptically, through an increase in K^+ conductance. These effects become apparent at higher doses than the presynaptic effects on C fiber-mediated responses (10,11). Thus, in the case of Aδ-mediated responses, the combination of ω-CTX acting presynaptically with the postsynaptic effect of morphine produces antinociception by two different, but complimentary mechanisms. Thus, morphine plus ω-CTX can produce a supraadditive antinociception, but only for Aδ-mediated responses. Consistent with this hypothesis, Omote et al. (19), demonstrated, isoboligraphically, a pharmacologic synergy between morphine and ω-CTX on the tail flick test. Given the likelihood that the tail flick test, as most typically administered, is Aδ mediated (20), the results presented here provide a clear indication that the synergy observed by Omote et al. is likely to occur for Aδ and not C fiber thermonociception.

The results described here indicate that although the addition of a Ca^{++} channel blocker to morphine can facilitate C fiber antinociception, the effect on Aδ-mediated nociception is much more dramatic. The administration of a minimally effective dose of ω-CTX with an essentially ineffective dose of morphine produced an increase in latency to the maximum allowed (cutoff) for responses to high rate skin heating. This clear supraadditivity implies that the combination of these two drugs might be useful in attenuating those types of pain that are likely to be dominated by Aδ nociceptors, such as some kinds of postsurgical pain. Furthermore, the capacity of giving these two drugs in such minimal doses should allow for optimal analgesia while minimizing adverse side effects of both of these drugs.

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tab C

US0058

United States Patent [19]

Phillips

[11] **Patent Number:** **5,840,737**

[45] **Date of Patent:** **Nov. 24, 1998**

[54] **OMEPRAZOLE SOLUTION AND METHOD FOR USING SAME**

[75] Inventor: **Jeffrey Owen Phillips**, Columbia, Mo.

[73] Assignee: **The Curators of the University of Missouri**, Columbia, Mo.

[21] Appl. No.: **680,376**

[22] Filed: **Jul. 15, 1996**

Related U.S. Application Data

[60] Provisional application No. 60/009,608, Apr. 4, 1996.

[51] **Int. Cl.**^{6} **A61K 31/44**

[52] **U.S. Cl.** **514/338**

[58] **Field of Search** **514/338**

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Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Kohn & Associates

[57] **ABSTRACT**

A pharmaceutical composition includes an aqueous solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof in a pharmaceutically acceptable carrier comprising a bicarbonate salt of a Group IA metal. A method for treating and/or preventing gastrointestinal conditions by administering to a patient a pharmaceutical composition including an aqueous solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal wherein the administering step consists of a single dosage form without requiring further administering of the bicarbonate salt of the Group IA metal. A pharmaceutical composition for making a solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof includes omeprazole or other substituted benzimidazoles and derivatives thereof and a bicarbonate salt of a Group IA metal in a form for convenient storage whereby when the composition is dissolved in aqueous solution, the resulting solution is suitable for enteral administration.

12 Claims, 1 Drawing Sheet

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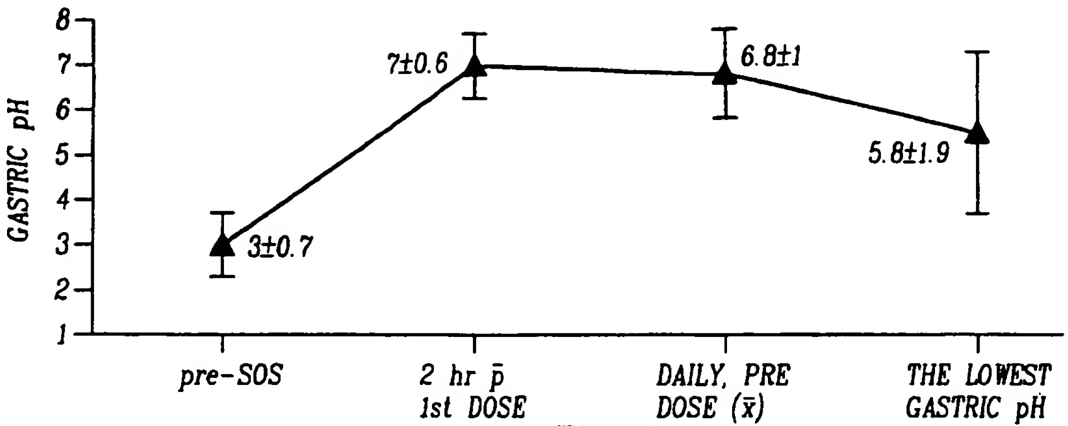
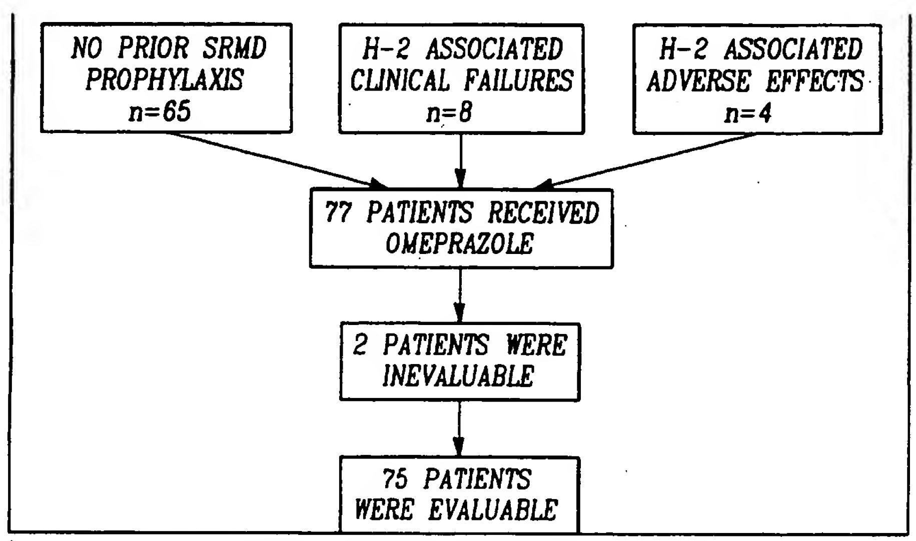


Fig-1



OVERALL PATIENT ENROLLMENT SCHEME

Fig-2

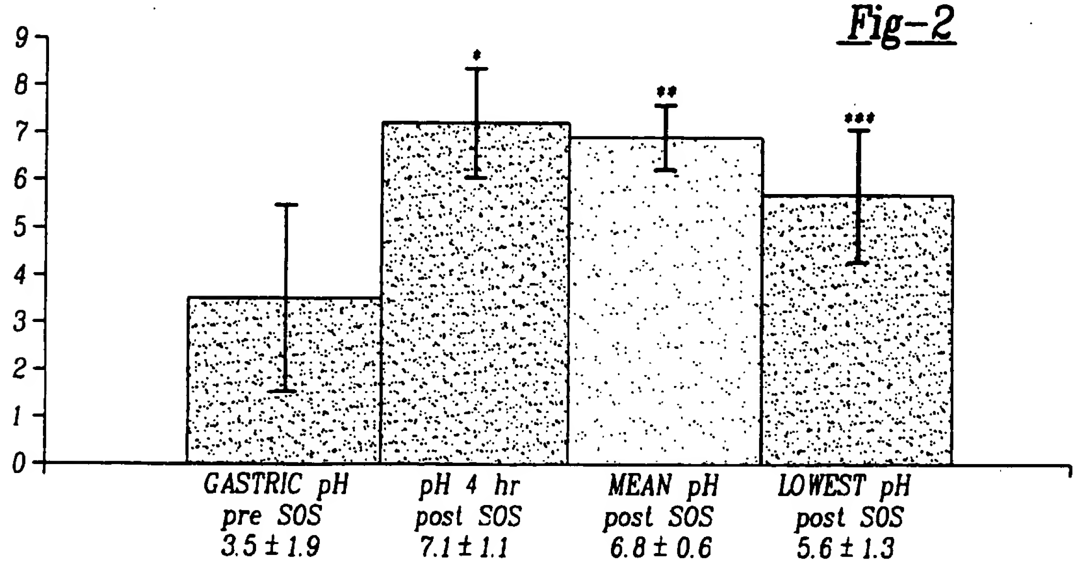


Fig-3

OMEPRAZOLE SOLUTION AND METHOD FOR USING SAME

This application is a continuation-in-part of U.S. Prov. App. Ser. No. 60/009,608 filed on Jan. 4, 1996.

TECHNICAL FIELD

The present invention relates to a pharmaceutical preparation containing a substituted benzimidazole. More particularly, the present invention relates to a substituted benzimidazole solution/suspension suitable for oral administration.

BACKGROUND OF THE INVENTION

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole, that inhibits gastric acid secretion. Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell.

Typically, omeprazole in the form of a delayed-release capsule, is prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors.

These above-listed conditions commonly arise in healthy or critically ill patients and may be accompanied by significant upper gastrointestinal bleeding. H_2 antagonists, antacids, and sucralfate are commonly administered to minimize the pain and the complications related to these conditions. These drugs have certain disadvantages associated with their use. Some of these drugs are not completely effective in the treatment of the aforementioned conditions and/or produce adverse side effects, such as mental confusion, constipation, diarrhea, thrombocytopenia, (lowered platelet count) and/or are relatively costly modes of therapy as they require the use of automated infusion pumps for continuous intravenous delivery.

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, 1984). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., 1981; Larson et al., 1984; Czaja et al., 1974; Skillman et al., 1969; and Cook et al., 1994). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., 1994). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., 1993). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., 1974; Peura and Johnson, 1985). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.

In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage is considered by many to be the standard of care (AMA Drug Evaluations). However, general consensus is lacking about which drugs to use in this setting (Martin et al., 1993; Gafter et al., 1989; Martin et al., 1992). In two recent meta-analyses (Cook et al., 1991; Tryba, 1994), antacids, sucralfate, and H_2-antagonists were all found to be superior to placebo and similar to one another in preventing upper gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in fifteen to twenty percent of patients in which they are employed because of failure to prevent bleeding, or control pH (Ostro et al., 1985; Siepler, 1986; Ballesteros et al., 1990), or because of adverse effects (Gafter et al., 1989; Sax, 1987; Vial et al., 1991; Cantu and Korek, 1991; Spychal and Wickham, 1985). In addition, the characteristics of an ideal agent for the prophylaxis of stress gastritis and concluded that none of the agents currently in use fulfill their criteria (Smythe and Zarowitz, 1994).

Omeprazole reduces gastric acid production by irreversibly inhibiting the H+/K+ ATPase of the parietal cell—the final common pathway for gastric acid secretion (Fellenius et al., 1981; Wallmark et al., 1985; Frylund et al., 1988). Because this drug maintains gastric pH control throughout the dosing interval and has a very good safety profile, it is a logical choice for stress ulcer prophylaxis. The absence of an intravenous or oral liquid dosage form in the United States, however, has limited the testing and use of omeprazole in the critical care patient population. Subsequently, Barie et al (Barie and Hariri, 1992) described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multi-organ failure.

Stress ulcer prophylaxis has become routine therapy in intensive care units in most hospitals (Fabian et al, 1993.; Cook et al., 1991). Controversy remains regarding pharmacologic intervention to prevent stress-related bleeding in critical care patients. It has been suggested that the incidence and risk of gastrointestinal bleeding has decreased in the last ten years and drug therapy may no longer be needed (Cook et al., 1994; Tryba, 1994; Schepp, 1993). This reasoning is not supported by a recent placebo-controlled study. Martin et al. conducted a prospective, randomized, double-blind, placebo-controlled comparison of continuous-infusion cimetidine and placebo for the prophylaxis of stress-related mucosal damage (Marten et al., 1993). The study was terminated early because of excessive bleeding-related mortality in the placebo group. It appears that the natural course of stress-related mucosal damage in a patient at risk who receives no prophylaxis remains significant. In the placebo group, thirty-three percent of patients developed clinically significant bleeding, nine percent required transfusion, and six percent died due to bleeding-related complications. In comparison, fourteen percent of cimetidine-treated patients developed clinically significant bleeding, six percent required transfusions, and 1.5% died due to bleeding-related complication; the difference in bleeding rates between treatment groups was statistically significant. This study clearly demonstrated that continuous-infusion cimetidine reduced morbidity in critical care patients. Although, these data were used to support the approval of continuous-infusion cimetidine by the Food and Drug Administration for stress ulcer

prophylaxis, H_2-antagonists fall short of being the optimal pharmacotherapeutic agents for preventing of stress-related mucosal bleeding.

Another controversy surrounding stress ulcer prophylaxis is which drug to use. In addition to the various H_2-antagonists, antacids and sucralfate are other treatment options for the prophylaxis of stress-related mucosal damage. An ideal drug in this setting should possess the following characteristics: prevent stress ulcers and their complications, be devoid of toxicity, lack drug interactions, be selective, have minimal associated costs (such as personnel time and materials), and be easy to administer (Smythe and Zarowitz, 1994).

Some have suggested that sucralfate is possibly the ideal agent for stress ulcer prophylaxis (Smythe and Zarowitz, 1994). Randomized, controlled studies support the use of sucralfate (Borrero et al., 1986; Tryba, 1987; Cioffi et al., 1994; Driks et al., 1987), but data on critical care patients with head injury, trauma, or burns are limited. In addition, a recent study comparing sucralfate and cimetidine plus antacids for stress ulcer prophylaxis reported clinically significant bleeding in three of forty-eight (6%) sucralfate-treated patients, one of whom required a gastrectomy (Cioffi et al., 1994). In the study performed by Driks and coworkers that compared sucralfate to conventional therapy (H_2-antagonists, antacids, or H_2-antagonists plus antacids), the only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm (Driks et al., 1987).

H_2-antagonists fulfill many of the criteria for an ideal stress ulcer prophylaxis drug. Yet, clinically significant bleeds can occur during H_2-antagonist prophylaxis (Martin et al., 1993; Cook et al., 1991; Schuman et al., 1987) and adverse events are not uncommon in the critical care population (Gafter et al., 1989; Sax, 1987, Vial et al., 1991; Cantu and Korek, 1991; Spychal and Wickham, 1985). One reason proposed for the therapeutic H_2-antagonist failures is lack of pH control throughout the treatment period (Ostro et al., 1985). Although the precise pathophysiologic mechanism(s) involved in stress ulceration are not clearly established, the high concentration of hydrogen ions in the mucosa (Fiddian-Green et al., 1987) or gastric fluid in contact with mucosal cells appears to be an important factor. A gastric pH >3.5 has been associated with a lower incidence of stress-related mucosal damage and bleeding (Larson et al., 1984; Skillman et al., 1969; Skillman et al., 1970; Priebe and Skillman, 1981). Several studies have shown that H_2-antagonists, even in maximal doses, do not reliably or continuously increase intragastric pH above commonly targeted levels (3.5 to 4.5). This is true especially when used in fixed-dose bolus regimens (Ostro, 1985; Siepler, 1986; Ballesteros et al., 1990). In addition, gastric pH levels tend to trend downward with time when using a continuous-infusion of H_2-antagonists, which may be the result of tachyphylaxis (Ostro et al., 1985; Wilder-Smith and Merki, 1992).

Because stress ulcer prophylaxis is frequently employed in the intensive care unit, it is essential from both a clinical and economic standpoint to optimize the pharmacotherapeutic approach. In an attempt to identify optimal therapy, cost of care becomes an issue. All treatment costs should be considered, including the costs of treatment failures and drug-related adverse events. While the actual number of failures resulting in mortality is low, morbidity (e.g., bleeding that requires blood transfusion) can be high, even though its association with the failure of a specific drug is often unrecognized.

Omeprazole represents an advantageous alternative to the use of H_2 antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage. However, in its current form (capsules containing an enteric-coated granule formulation of omeprazole), omeprazole can be difficult or impossible to administer to patients who are unable (critically ill patients, children, elderly, patients suffering from dysphagia) or patients who are either unwilling or unable to swallow tablets or capsules. Therefore, it would be desirable to formulate an omeprazole solution which can be enterally delivered to a patient thereby providing the benefits of omeprazole without the drawbacks of the current capsule dose form.

Omeprazole has been formulated in many different embodiments such as in a mixture of polyethylene glycols formed a mixture of adeps solidus and sodium lauryl sulfate in a soluble, basic amino acid to yield a formulation designed for administration in the rectum as shown in U.S. Pat. No. 5,219,870 to Kim. U.S. Pat No. 5,395,323 to Berglund ('323) discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient. The '323 patent teaches the use of an omeprazole tablet which is placed in the device and dissolved by normal saline, and infused into the patient. This device and method of infusing omeprazole does not provide the omeprazole solution as an enteral product nor is this omeprazole solution directly administered to the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate anti-acid effect of the present formulation.

U.S. Pat. No. 4,786,505 to Lovgren et al., discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH. The powder mixture is then formulated to small beads, pellets, tablets and may be loaded into capsules by conventional pharmaceutical procedures.

This formulation of omeprazole does not provide an omeprazole dose form which can be enterally administered to a patient who may be unable and/or unwilling to swallow capsules or pellets nor does it teach a convenient form which can be used to make an omeprazole solution.

Several buffered omeprazole solutions have been disclosed. Andersson et al., 1993; Landahl et al., 1992; Andersson et al., 1990; Regardh et al., 1990; Andersson et al., 1990; Pilbrant et al., 1985.

All of the buffered omeprazole solutions described in these references were administered orally and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration.

In all of these studies, repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration. As a result, the ingestion of the large amounts of sodium bicarbonate and large volumes of water were required. In the above-cited studies, as much as 48 mmoles of sodium bicarbonate in 300 ml of water must be ingested for a single dose of omeprazole to be orally administered.

Initial reports of increased frequency of pneumonia in patients receiving stress ulcer prophylaxis with agents that raise gastric pH has influenced the pharmacotherapeutic approach to management of critical care patients. However, several recent studies (Simms et al., 1991; Pickworth et al., 1993; Ryan et al., 1993; Fabian et al., 1993), a meta-analysis (Cook et al., 1991), and a closer examination of the studies that initiated the elevated pH-associated pneumonia hypotheses (Schepp, 1993) cast doubt on a causal relationship. The relationship between pneumonia and antacid therapy is much stronger than for H_2-antagonists. The shared effect of antacids and H_2-antagonists on gastric pH seems an irresistible common cause explanation for nosocomial pneumonia observed during stress ulcer prophylaxis. However, there are important differences between these agents that are not often emphasized (Laggner et al., 1989). When antacids are exclusively used to control pH in the prophylaxis of stress-related upper gastrointestinal bleeding, large volumes are needed. Volume, with or without subsequent reflux, may be the underlying mechanism(s) promoting the development of pneumonia in susceptible patient populations rather than the increased gastric pH. The rate of pneumonia in our study (12%) was not unexpected in this critical care population and compares with sucralfate, which does not significantly raise gastric pH (Pickworth et al., 1993; Ryan et al., 1993).

The buffered omeprazole solutions of the above cited prior art require large amounts of sodium bicarbonate to be given by repeated administration. This is necessary to prevent acid degradation of the omeprazole. The administration of large amounts of sodium bicarbonate can produce at least four significant adverse effects which can dramatically reduce the efficacy of the omeprazole in patients and reduce the overall health of the patients. In the above-cited studies, basically healthy volunteers rather than sick patients were given only one or two dosages of omeprazole utilizing pre-dosing and post-dosing with large volumes of sodium bicarbonate. This dosing protocol would not be suitable for sick or critically ill patients who must receive multiple doses of omeprazole.

Since bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their gastroesophageal reflux disease as the belching can cause upward movement of stomach acid (Brunton, 1990).

Patients with conditions, such as hypertension or heart failure, are standardly advised to avoid the intake of excessive sodium as this can cause aggravation or exacerbation of their hypertensive conditions (Brunton, 1990).

Additionally, patients with numerous conditions which typically accompany critical illness should avoid the intake of excessive sodium bicarbonate as it can cause metabolic alkalosis which can result in a serious worsening of the patient's condition. Furthermore, excessive antacid intake (such as sodium bicarbonate) can result in drug interactions which produce serious adverse effects. For example, by altering gastric and urinary pH, antacids can alter rates of drug dissolution and absorption, bioavailability, and renal elimination (Brunton, 1990).

Since buffered omeprazole solution requires prolonged administration of the antacid, sodium bicarbonate, it makes it difficult for patients to comply with the above recommendation.

In addition to the disadvantages associated with excessive intake of sodium bicarbonate, the above-cited prior art teaches a relatively complex regimen for the oral administration of omeprazole. For example, in the Pilbrant et al. (1985) reference, the oral omeprazole administration protocol calls for administering to a subject who has been fasting for at least ten hours, a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later, the subject ingests a suspension of 60 mg of omeprazole in 50 ml of water which also contains 8 mmoles of sodium bicarbonate. This is rinsed down with another 50 ml of 8 mmoles sodium bicarbonate solution. Ten minutes after the ingestion of the omeprazole dose, the subject ingests 50 ml of bicarbonate solution (8 mmoles). This is repeated at twenty minutes and thirty minutes post omeprazole dosing to yield a total of 48 mmoles of sodium bicarbonate and 300 ml of water in total which are ingested by the subject for a single omeprazole dose.

Not only does this regimen require the ingestion of excessive amounts of bicarbonate and water, it is unlikely that a healthy patient would comply with this regimen for each dose of omeprazole over the course of a prescribed omeprazole protocol. It is unlikely or even improbable that a critically ill patient would be able to comply with this regimen.

Even in healthy patients, the complexity of the drug regimen leads to the conclusion that patients would be unlikely to comply with this regimen thereby leading to a lack of beneficial outcome for the patient. It is well documented that patients who are required to follow complex schedules for drug administration are non-compliant and, thus, the efficacy of the buffered omeprazole solutions of the prior art would be expected to be reduced due to non-compliance. Compliance has been found to be markedly reduced when patients are required to deviate from a schedule of one or two (usually morning and night) doses of a medication per day. The use of the prior art buffered omeprazole solutions which require administration protocols with numerous steps, different drugs (sodium bicarbonate+omeprazole+PEG400 versus sodium bicarbonate alone), and specific time allotments between each stage of the total omeprazole regimen in order to achieve efficacious results is clearly in contrast with both current drug compliance theories and human nature.

The prior art (Pilbrant et al., 1985) teaches that the buffered omeprazole suspension can be stored at refrigerator temperatures for a week and deep frozen for a year while still maintaining 99% of their initial potency. It would be desirable to have an omeprazole solution which could be stored at room temperature or in a refrigerator for periods of time which exceed those of the prior art while still maintaining 99% of the initial potency. Additionally, it would be advantageous to have a form of the omeprazole and bicarbonate which can be utilized to instantly make the omeprazole solution/suspension of the present invention which is supplied in a solid form which imparts the advantages of improved shelf-life at room temperature, lower cost to produce, less expensive shipping costs, and which is less expensive to store.

It would, therefore, be desirable to have an omeprazole formulation which provides a cost effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonist, antacids, and sucralfate. Further, it would be desirable to have an omeprazole formulation which is convenient to prepare and administer to patients unable ingest capsules, which is rapidly absorbed, can be enterally delivered directly to the desired treatment region, which does not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an antacid immediately upon delivery. Furthermore, it would be desirable to have a pharmaceutical

composition which is highly efficacious for the treatment of the aforementioned conditions.

The present invention provides a solution/suspension of omeprazole, lansoprazole or other suitable benzimidazoles which is suitable for enteral administration which includes all of the aforementioned advantages.

SUMMARY OF THE INVENTION AND ADVANTAGES

In accordance with the present invention, there is provided a pharmaceutical composition including an aqueous solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal.

The present invention further provides a method for treating and/or preventing gastrointestinal conditions by administering to a patient a pharmaceutical composition including an aqueous solution/suspension of omeprazole and derivatives thereof in a pharmaceutically acceptable carrier comprising a bicarbonate salt of a Group IA metal wherein the administration step consists of a single dosage without requiring further administration of the bicarbonate salt of the Group IA metal.

The present invention further provides a pharmaceutical composition for use making a solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

FIG. 1 is a graph showing the effect of the omeprazole solution/suspension of the present invention on gastric pH in patients at risk for upper gastrointestinal bleeding from stress-related mucosal damage;

FIG. 2 is a flow chart illustrating a patient enrollment scheme; and

FIG. 3 is a bar graph illustrating gastric pH both pre- and post- administration of omeprazole solution/suspension according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

A pharmaceutical composition which can include an aqueous solution/suspension of omeprazole or other substituted benzimidazoles such as lansoprazole, and derivatives thereof in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal is disclosed. For the purposes of description, the composition includes both solutions and/or suspensions of the omeprazole or other substituted benzimidazoles. Hereinafter, the use of the term "solution" includes solutions and/or suspensions of the substituted benzimidazoles.

The pharmaceutical composition of the present invention is prepared by mixing omeprazole (Merck & Co. Inc., West Point, Pa.) or other substituted benzimidazoles and derivatives thereof with a solution including a bicarbonate salt of a Group IA metal. Preferably, omeprazole powder or granules, which can be obtained from a capsule, are mixed with a sodium bicarbonate solution to achieve a desired final omeprazole concentration. The concentration of omeprazole in the solution/suspension can range from approximately 0.5 mg/ml to approximately 6.0 mg/ml. The preferred concentration for the omeprazole in the solution/suspension ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml with 2 mg/ml being the standard concentration.

The pharmaceutically effective carrier includes the bicarbonate salt of the Group IA metal and can be prepared by mixing the bicarbonate salt of the Group IA metal, preferably sodium bicarbonate, with water. The concentration of the bicarbonate salt of the Group IA metal in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt of the Group IA metal ranges from approximately 7.5 percent to approximately 10.0 percent. In a preferred embodiment of the present invention, sodium bicarbonate is the preferred salt of the Group IA metal and is present in a concentration of approximately 8.4 percent.

In a preferred embodiment of the present invention, enterically-coated omeprazole particles are obtained from delayed release capsules (Astra Merck) additionally omeprazole powder can be used. The coated omeprazole particles are mixed with a sodium bicarbonate ($NaHCO_3$) solution which dissolves the enteric coating and forms an omeprazole solution/suspension in accordance with the present invention. It is important to emphasize that the enteric coated pellets of omeprazole must be allowed to completely breakdown in the suspension vehicle or carrier prior to administration. The omeprazole solution/suspension has significant pharmacokinetic advantages over standard time-release omeprazole capsules including: a decreased drug absorbance time (~10 to 12 minutes) following administration for the omeprazole solution versus (~2–3 hours) following administration for the enteric coated pellets; the $NaHCO_3$ solution protects the omeprazole from acid degradation prior to absorption; the $NaHCO_3$ acts as an antacid while the omeprazole is being absorbed; and the solution/suspension can be administered through an existing indwelling tube without clogging, for example, nasogastric or other feeding tubes (jejunal or duodenal) including small bore needle catheter feeding tubes.

As stated above, suitable derivatives of omeprazole can be substituted for the omeprazole or other suitable substituted benzimidazoles without departing from the spirit of the present invention. These derivatives can include, but are not limited to, lansoprozole.

The pharmaceutical composition including the omeprazole and derivatives thereof in a pharmaceutically acceptable carrier of a bicarbonate salt of Group IA metal can be used for the treatment of gastrointestinal conditions including, but not limited to, active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison Syndrome. These conditions are caused by imbalances between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. Treatment of these conditions is accomplished by administering to a patient an effective amount of the pharmaceutical composition according to the present invention.

The omeprazole solution/suspension is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the sight and method of administration, scheduling of administration, and other factors known to medical practitioners. The "effective amount" for purposes herein thus

determine by such considerations as are known in the art. The amount must be effective to achieve improvement, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood transfusion, improved survival rate, more rapid recovery, or improvement or elimination of systems and other indicators as are selected as appropriate measures by those skilled in the art.

The dosage range of omeprazole or other substituted benzimidazoles and derivatives thereof can range from approximately 2 mg/day to approximately 100 mg/day. The standard daily dosage is typically 20 mg omeprazole in 10 ml of solution.

In the method of the present invention, the omeprazole solution/suspension can be administered in various ways. It should be noted that the omeprazole solution/suspension can be administered as the compound or as the pharmaceutically acceptable salt and can be administered alone or in combination with pharmaceutically acceptable carriers. The compounds can be administered orally or enterally. The formulations can be made more palatable by adding flavorings such as chocolate, root beer, and others.

Additionally, various additives including ambicin which enhance the stability, sterility, and isotonicity of the compositions. Additionally, antimicrobial preservatives, antioxidants, chelating agents, and buffers can be added. However, microbiological evidence shows that this formulation inherently possesses anti-microbial activity. Prevention of the action of microorganisms can be enhanced by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like.

In many cases, it would be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Additionally, thickening agents, such as methyl cellulose, in order to reduce settling the omeprazole or derivatives thereof from the suspension.

The formulations of the present invention can be manufactured in a concentrated form, such as an effervescent tablet, so that upon reaction with water, the aqueous form of the present invention would be produced for oral or enteral administration.

Additionally, the present invention can be manufactured by utilizing micronized omeprazole in place of the omeprazole granules or omeprazole powder in place of omeprazole granules. This process is known as micronization and is utilized in order to produce a particle having a greater diameter. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate.

Although micronization results in increased surface area causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole.

A pharmacological formulation of the omeprazole solution/suspension utilized in the present invention can be administered orally to the patient. A pharmacological formulation of the omeprazole solution/suspension utilized in the present invention is preferably administered enterally. This can be accomplished, for example, by administering the solution/suspension via a nasogastric tube or other indwelling tubes. In order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the omeprazole solution of the present invention is administered in a single dose which does not require any further administration of bicarbonate following the administration of the omeprazole solution. That is, unlike the prior art omeprazole solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose which does not require administration of bicarbonate either before administration of the omeprazole or after administration of the omeprazole. The present invention eliminates the need to pre- or post-dose with additional volumes of water and sodium bicarbonate. The amount of bicarbonate administered via the single dose administration of the present invention is less than the amount of bicarbonate administered as taught in the prior art references cited above.

The amount of sodium bicarbonate used in the solution/suspension of the present invention is approximately 1 meq (or mmole) sodium bicarbonate per 2 mg omeprazole, with a range of approximately 0.75 meq (mmole) to 1.5 meq (mmole) per 2 mg of omeprazole.

The present invention further includes a pharmaceutical composition for making a solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof, which consists essentially of omeprazole or other substituted benzimidazoles and derivatives thereof and a bicarbonate salt of a Group IA metal in a form convenient for storage, whereby when the composition is placed into a aqueous solution, the composition dissolves yielding a solution/suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution in the aqueous solution. The omeprazole or other substituted benzimidazoles and derivatives thereof and bicarbonate can be formed into a tablet, capsules, or granules, by methods well known to those skilled in the art.

The pharmaceutical composition suitable for making a solution/suspension according to the present invention can further include an effervescing agent to aid in the dissolution of the pharmaceutical composition in the aqueous solution. In the present invention the effervescing agent is sodium bicarbonate.

The resultant omeprazole solution is stable at room temperature for several weeks and inhibits the growth of bacteria or fungi as shown in Example IV below. By providing a pharmaceutical composition including the omeprazole or other substituted benzimidazole and derivatives thereof with bicarbonate in a solid form, which is dissolved in a prescribed amount of aqueous solution to yield the desired concentration of omeprazole and bicarbonate, the cost of production, shipping, and storage are greatly reduced as no liquids are shipped (reducing weight and cost) and there is no need to refrigerate the solid form of the composition or the solution. The resultant solution, can be formulated and then used to provide dosages for a single patient over a course of time or for several patients.

The following experimental data illustrate the utility of the pharmaceutical composition of the present invention.

METHODS

EXAMPLE I

Patients were evaluable if they met the following criteria: had two or more risk factors for SRMD (mechanical ventilation, head injury, severe burn, sepsis, multiple trauma, adult respiratory distress syndrome, major surgery, acute renal failure, multiple operative procedures, coagulatherapy, significant hypotension, acid-base disorder, and hepatic failure), gastric pH of ≦4 prior to study entry, and no concomitant prophylaxis for SRMD.

Nasogastric (ng) tubes were placed in the patients and an omeprazole dosage protocol of 40 mg omeprazole solution/suspension followed by 40 mg omeprazole solution/suspension in eight hours, then 20 mg omeprazole solution/suspension per day, for five days. After each omeprazole solution/suspension administration, nasogastric suction was turned off for thirty minutes.

Results

Eleven patients were evaluable. All patients were mechanically ventilated. Two hours after the initial dose of omeprazole solution/suspension 40 mg omeprazole, all patients had an increase in gastric pH to greater than eight as shown in FIG. 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four on 20 mg omeprazole solution/suspension. One patient required 40 mg omeprazole solution/suspension per day (closed head injury, five total risk factors for SRMD). Two patients were changed to omeprazole solution/suspension after having developed clinically significant upper gastrointestinal bleeding while receiving conventional intravenous H_2 antagonists. Bleeding subsided in both cases after twenty-four hours. Clinically significant upper gastrointestinal bleeding did not occur in the other nine patients. Overall mortality was 27%, mortality attributable to upper gastrointestinal bleeding was 0%. Pneumonia developed in one patient after initiating omeprazole therapy and was present upon the initiation of omeprazole therapy in another patient. The mean length of prophylaxis was five days.

A pharmacoeconomic analysis revealed a difference in the total cost of care for the prophylaxis of SRMD:

- ranitidine (Zantac®) continuous infusion intravenously (150 mg/24 hours)×five days $125.50;
- cimetidine (Tagamet®) continuous infusion intravenously (900 mg/24 hours)×five days $109.61;
- sucralfate one gm slurry four times a day per (ng) tube×five days $73.00; and
- SOS regimen per (ng) tube×five days $65.70.

Conclusion

This example illustrates the efficacy of the simplified omeprazole solution of the present invention based on the increase in gastric pH, safety and cost/convenience of the omeprazole solution/suspension as a method for SRMD prophylaxis.

EXAMPLE II

Experiments were carried out in order to determine the effect of the omeprazole solution/suspension (omeprazole/sodium bicarbonate solution) administration on the accuracy on subsequent pH measurements through a nasogastric tube.

Methods

The omeprazole solution/suspension was prepared by mixing 10 ml of 8.4% sodium bicarbonate with the contents of a 20 mg capsule of omeprazole (Merck & Co. Inc., West Point, Pa.) to yield a solution/suspension having a final omeprazole concentration of 2 mg/ml. After mixing the omeprazole solution/suspension, it was administered into the stomach, usually, through a nasogastric (ng) tube. Nasogastric tubes from nine different institutions were gathered for an evaluation 400 mg omeprazole solution/suspension was prepared as described above. Artificial gastric fluid (gf) was prepared according to the USP. pH recordings were made in triplicate using a Microcomputer Portable pH meter model 6007 (Jenco Electronics Ltd., Taipai, Taiwan). [1] First the terminal portion (tp) of the nasogastric tubes was placed into a glass beaker containing the gastric fluid. A 5 ml aliquot of gastric fluid was aspirated through each tube and the pH recorded, this was called the "pre-omeprazole solution/suspension measurement". [2] Secondly, the terminal portion (tp) of each of the nasogastric tubes was removed from the beaker of gastric fluid and placed into an empty beaker. Twenty (20) mg of omeprazole solution/suspension was delivered through each of the nasogastric tubes and flushed with 10 ml of tap water. The terminal portion (tp) of each of the nasogastric tubes was placed back into the gastric fluid. After a one hour incubation, a 5 ml aliquot of gastric fluid was aspirated through each nasogastric tube and the pH recorded, this was called the "after 1st dose SOS measurement". [3] After an additional hour had passed, the second step was repeated, this was called the "after 2nd ND dose SOS measurement". In addition to the pre-SOS measurement, the pH of the gastric fluid was checked in triplicate after steps [2] and [3]. A change in the pH measurements of ±0.3 units was considered significant. The Friedman test was used to compare the results. The Friedman test is a two way analysis of variance which is used when more than two related samples are of interest, as in repeated measurements.

Results

The results of this experiments are outlined in Table 1. Table 1 illustrates the results of the pH measurements that were taken during the course of the experiment. These results illustrate that there were no statistically significantly latent effects of omeprazole solution/suspension administration (per nasogastric tube) on the accuracy of subsequent pH measurements obtained through the same nasogastric tube.

EXAMPLE III

Experiments were performed in order to determine the efficacy, safety, and cost of simplified omeprazole suspension in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Methods

Patients

Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage. Interventions: Patients received 20 ml omeprazole suspension (containing 40 mg of omeprazole) initially, followed by a second 20 ml dose six-eight hours later, then 10 ml (20 mg) daily. Omeprazole solution/suspension according to the present invention was administered through a nasogastric tube, followed by 5–10 ml of tap water. The nasogastric tube was clamped for one-two hours after each administration.

Measurements and Main Results

The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage and was associated with a five percent decrease in hematocrit. Secondary efficacy measures were gastric pH measured four hours after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the incidence of adverse events and the incidence of pneumonia. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric pH was 7.1 (mean), the mean gastric pH after starting omeprazole was 6.8 (mean) and the lowest pH after starting omeprazole was 5.6 (mean). The incidence of pneumonia was twelve percent. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions

Omeprazole suspension prevented clinically significant upper gastrointestinal bleeding and maintained gastric pH above 5.5 in mechanically ventilated critical care patients without producing toxicity.

Materials and Methods

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population

All adult (>18 years old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated intensive care unit stay of at least forty-eight hours were considered for inclusion in the study. To be included patients also had to have a gastric pH of <4, had to be mechanically ventilated and have one of the following additional risk factors for a minimum of twenty-four hours after initiation of omeprazole suspension: head injury with altered level of consciousness, extensive burns (>20% Body Surface Area), acute renal failure, acid-base disorder, multiple trauma, coagulopathy, multiple operative procedures, coma, hypotension for longer than one hour or sepsis (see Table 2). Sepsis was defined as the presence of invasive pathogenic organisms or their toxins in blood or tissues resulting in a systematic response that included two or more of the following: temperature greater than 38° C. or less than 36° C., heat rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute (or $_pO_2$ less than 75 mm Hg), and white blood cell count greater than 12,000 or less than 4000 cells/mm^3 or more than 10 percent bands (Bone, 1991). Patients in whom H_2-antagonist therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count less than 30,000 cells/mm ^{3}); were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH above four for forty-eight hours after ICU admission (without prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having non-stress-related mucosal bleeding. The reason for this exclusion is the confounding effect of non-stress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration

Omeprazole solution/suspension was prepared immediately before administration by the patient's nurse using the following instructions: 1) Empty the contents of one or two 20 mg omeprazole capsule(s) into an empty 10 ml syringe (with 20 gauge needle in place) from which the plunger has been removed. (Omeprazole delayed-release capsules, Merck & Co., Inc., West Point, Pa.). 2) Replace the plunger and uncap the needle. 3) Withdraw 10 ml of 8.4% sodium bicarbonate solution or 20 ml if 40 mg given (Abbott Laboratories, North Chicago, Ill.). The resultant preparation should contain 2 mg omeprazole per ml of 8.4% sodium bicarbonate. 4) Allow the enteric coated pellets of omeprazole to completely breakdown, ~30 minutes (agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before using. The solution/suspension was not administered with acidic substances. A high pressure liquid chromatography study was performed that has demonstrated that this preparation of simplified omeprazole suspension maintains >90% potency for seven days at room temperature. This preparation remained free of bacterial and fungal contamination for thirty days when stored at room temperature (see Table 5).

The initial dose of omeprazole solution/suspension was 40 mg, followed by a second 40 mg dose 6–8 hours later, then a 20 mg daily dose administered at 8:00 AM. Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5–10 ml of tap water and clamped for at least one hour. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube removed and the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures

The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-minute lavage or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, Calif.) positive coffee ground material for four consecutive hours that did not clear with lavage (at least 100 ml) and produced a 5% decrease in hematocrit.

Secondary Outcome Measures

The secondary efficacy measures were gastric pH measured four hours after omeprazole was administered, mean gastric pH after starting omeprazole and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, N.Y.) was used to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of one pH unit. Gastric pH was measured before the initiation of omeprazole solution/suspension therapy, immediately before each dose, and every four hours between doses.

Other secondary outcome measures were incidence of adverse events (including drug interactions) and pneumonia. Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Prevention and Control definition of nosocomial pneumonia (Garner et al., 1988). According to these criteria, a patient who has pneumonia is one who has rales or dullness to percussion on physical examination of the chest or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and has at least two of the following present: new purulent sputum or changes in character of the sputum, an organism isolated from blood culture, fever or leukocytosis, or evidence of infection from a protective specimen brush or bronchoalveolar lavage. Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia incidence figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present prior to the start of omeprazole suspension.

Cost of Care Analysis

A pharmacoeconomic evaluation of stress ulcer prophylaxis using omeprazole solution/suspension was performed. The evaluation included total drug cost (acquisition and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental confusion), costs associated with clinically significant upper gastrointestinal bleeding. Total drug cost was calculated by adding the average institutional costs of omeprazole 20 mg capsules, 50 ml sodium bicarbonate vials, and 10 ml syringes with needle; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

Statistical Analysis

The paired t-test (two-tailed) was used to compare gastric pH before and after omeprazole solution/suspension administration and to compare gastric pH before omeprazole solution/suspension administration with the mean and lowest gastric pH value measured after beginning omeprazole.

Results

Seventy-seven patients met the inclusion and exclusion criteria and received omeprazole solution/suspension (see FIG. 2). Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down prior to the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above six as soon as the patient was given a dose of omeprazole solution/suspension (in which the enteric coated pellets of omeprazole had been allowed to completely breakdown).

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose 20 was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained above four in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared failures, their pH values were no longer followed.

The ages of the remaining seventy-five patients ranged from eighteen to eighty-seven years; forty-two patients were male and thirty-three were female. All patients were mechanically ventilated during the study. Table 2 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was two to ten, with a mean of 3 (±1) (standard deviation). Five patients enrolled in the study had developed clinically significant bleeding while receiving continuous infusions of ranitidine (150 mg/24 hr) or cimetidine (900 mg/24 hr). In all five cases, the bleeding subsided and the gastric pH rose to above five within thirty-six hours after initiating omeprazole therapy. Three patients were enrolled after having developed two consecutive gastric pH values below three while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH rose to above five within four hours after omeprazole therapy was initiated. Four other patients were enrolled in this study after experiencing confusion (n=2) or thrombocytopenia (n=2) during H_2-antigens therapy. Within thirty-six hours of switching therapy, these adverse events resolved.

Stress-related Mucosal Bleeding and Mortality

None of the sixty-five patients who received simplified omeprazole suspension as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only (Gastroccult-positive) within eighteen hours of starting omeprazole suspension; bleeding stopped in all patients within thirty-six hours. The overall mortality rate in this group of critically ill patients was eleven percent. No death was attributable to upper gastrointestinal bleeding or the use of omeprazole solution/suspension.

Gastric pH

The mean (±standard deviation) pre-omeprazole gastric pH was 3.5±1.9. Within four hours of omeprazole administration, the gastric pH rose to 7.1±1.1 (se FIG. 3); this difference was significant ($p<0.001$). The differences between pre-omeprazole gastric pH and the mean and lowest gastric pH measurements during omeprazole administration (6.8±0.6 and 5.6±1.3, respectively) were also statistically significant ($p<0.001$).

Safety

Omeprazole solution/suspension was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have been drug-related thrombocytopenia. However, the platelet count continued to fall after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus was unable to continue on omeprazole. No clinically significant drug interactions with omeprazole were noted during the study period. As stated above, metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in omeprazole solution/suspension was small (~12 mEq/10 ml) and no electrolyte abnormalities were found.

Pneumonia

Pneumonia developed in nine (12%) patients receiving omeprazole solution/suspension. Pneumonia was present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic evaluation

The average length of treatment was nine days. The cost of care data are listed in Tables 3 and 4. The costs of drug acquisition, preparation, and delivery for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 3. There were no costs to add from toxicity associated with omeprazole solution/suspension. Since two of seventy-five patients required 40 mg of omeprazole solution/suspension daily to adequately control gastric pH, the acquisition/preparation cost should reflect this. The additional 20 mg of omeprazole with vehicle adds seven cents per day to the cost of care. Therefore, the daily cost of care for omeprazole solution/suspension in the prophylaxis of stress-related mucosal bleeding was $12.60 see Table 4.

Omeprazole solution/suspension is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has been challenged recently (6). All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage—mechanical ventilation. Previous trials and data from a recently published study show that stress ulcer prophylaxis is of proven benefit in patients at risk and, therefore, it was thought to be unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during omeprazole solution/suspension therapy. Gastric pH was maintained above 4 on omeprazole 20 mg/day in seventy-three of seventy-five patients. No adverse events or drug interaction associated with omeprazole were encountered.

EXAMPLE IV

The anti-microbial or bacteriostatic effects of the omeprazole solution/suspension were analyzed by applicants.

TABLE 1

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
[1] gf Pre SOS	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[2] gf p 1st dose	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
1.3←check of fg pH									
[3] gf p 2nd dose	1.3	1.3	1.4	1.4	1.4	1.3	1.4	1.3	1.3
1.3←check of gf pH						SOS pH = 9.0			

TABLE 2

Mech Vent	Major Surgery	Multi-trauma	Head Injury	Hypo-tension	Renal Failure	Sepsis	Multiple Operation	Acid/Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2

Risk factors present in patients in this study (n = 75)

An omeprazole solution/suspension made according to the present invention was stored at room temperature for four weeks and then was analyzed for fungal and bacterial growth.

Results

Following four weeks of storage at room temperature, no bacterial or fungal growth was detected.

An omeprazole solution/suspension made in accordance with the present invention was stored at room temperature for twelve weeks and then was analyzed for fungal and bacterial growth.

Results

After twelve weeks of incubation at room temperature, no fungal or bacterial growth was detected.

The results of these experiments illustrate the stability and bacteriostatic characteristics of the omeprazole solution/suspension of the present invention.

Throughout this application various publications and patents are referenced by citation and number. Full citations for the publication are listed below. The disclosure of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, reference numerals are merely for convenience and are not to be in any way limiting, the invention may be practiced otherwise than as specifically described.

TABLE 3

		Per day
RANITIDINE (day 1–9)		
Ranitidine	150 mg/24 hr	6.15
Ancillary Product (1)	Piggyback (60%)	0.75
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs × 50%	14.50
TOTAL for 9 days	→	304.20
RAINITIDINE Cost per day	→	33.80
CIMETIDINE (day 1–9)		
Cimetidine	900 mg/24 hr	3.96
Ancillary Product (1)	Piggyback	1.25
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs × 50%	14.50
TOTAL for 9 days	→	288.99
CIMETIDINE Cost per day	→	32.11
SUCRALFATE (day 1–9)		
Sucralfate	1 Gm × 4	2.40
Ancillary Product (1)	syringe	.20
Sterile Prep required	no	
R.N. time ($24/hr)	30 minutes/day (includes pH monitoring)	12.00
TOTAL for 9 days	→	131.40

TABLE 3-continued

	Per day
SUCRALFATE Cost per day →	14.60

Note:
Does not include the cost of failure and/or adverse effect.
Acquisition, preparation and delivery costs of traditional agents.

TABLE 4

The average length of treatment was 9 days. Cost of care was calculated from these data:

		Per day	Total
OMEPRAZOLE (day 1)			
Product acquisition cost	40 mg load × 2 (5.66/dose)	11.32	11.32
Ancillary product	materials for solution preparation	0.41	0.41
Ancillary product	syringe w/needle	0.20	0.40
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
OMEPRAZOLE (days 2–9)			
Product acquisition cost	20 mg per day	2.83	22.65
Ancillary product	materials for solution preparation	0.41	0.82
Ancillary product	syringe w/needle	0.20	1.60
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	18 minutes/day (includes pH monitoring)	8.40	57.60
2/75 patient require 40 mg simplified omeprazole solution per day (days 2–9)			0.63
No additional cost for adverse effects or for failure			
TOTAL →			113.43
Simplified Omerprazole Solution Cost per day →			12.60

Pharmacoeconomic evaluation of omeprazole cost of care

TABLE 5

Time	Control	1 hour	24 hour	2 day	7 day	14 day
Conc(mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

Stability of Simplified Omeprazole Solution at room temperature (25° C.)
Values are the mean of three samples

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We claim:

1. A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole or lansoprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or, suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal.

2. A method according to claim 1, wherein the Group IA metal is sodium.

3. A method according to claim 1, wherein the Group IA metal is potassium.

4. A method according to claim 1, wherein the concentration of omeprazole in the composition range from approximately 0.5 mg/ml to approximately 6.0 mg/ml.

5. A method according to claim 3, wherein the concentration of omeprazole in said composition range from approximately 1.0 mg/ml to approximately 4.0 mg/ml.

6. A method as set forth in claim 5, wherein the concentration of omeprazole in the composition is approximately 2.0 mg/ml.

7. A method as set forth in claim 1, wherein the concentration of the bicarbonate salt of the Group IA metal in the composition ranges from approximately 5.0% to approximately 60.0%.

8. A method as set forth in claim 7, wherein the concentration of the bicarbonate salt of the Group IA metal in the

composition ranges from approximately 7.5% to approximately 10.0%.

9. A method as set forth in claim 8, wherein the concentration of the bicarbonate salt of the Group IA metal is approximately 8.4%.

10. A method as set forth in claim 1, wherein the single dosage form includes a concentration of bicarbonate ranging from approximately 0.75 meq to 1.5 meq per milliliter.

11. A method as set forth in claim 10, wherein the amount of the bicarbonate in the single dosage form is less than approximately 12 mEq/20 mg dose of omeprazole.

12. A method as set forth in claim 1, wherein the single dosage form is administered in a volume of between approximately 10 ml and 20 ml.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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INVENTOR(S) : Jeffrey Owen Phillips

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

On the title page,
first column, Item [60] "April 4,1996" should read -- Jan. 4,1996--.

Signed and Sealed this

Twenty-fifth Day of May, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

(12) **United States Patent**
Phillips

(10) **Patent No.: US 6,489,346 B1**
(45) **Date of Patent: *Dec. 3, 2002**

(54) **SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHOD OF USING SAME**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

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(51) **Int. Cl.**^{7} **C07D 401/12**; A61K 31/4439

(52) **U.S. Cl.** **514/338**; 514/395; 546/273.7; 548/307.1

(58) **Field of Search** 514/338, 395; 546/273.7; 548/307.1

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(57) **ABSTRACT**

There is provided a solid pharmaceutical composition in a dosage form that is not enteric-coated, having active ingredients including a non-enteric coated proton pump inhibitor and at least one buffering agent. The proton pump inhibitor is omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and the buffering agent is in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor. The dosage form includes a suspension tablet, a chewable tablet, an effervescent powder, or an effervescent tablet. Also provided is a method for treating an acid-related gastrointestinal disorder in a subject in need thereof by administering to the subject a solid pharmaceutical composition.

118 Claims, 2 Drawing Sheets

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FIG. 1

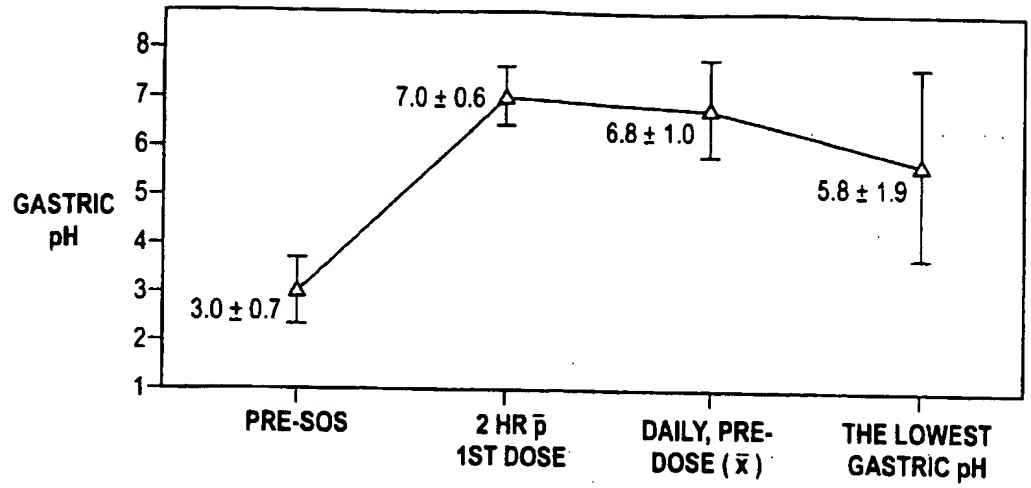

GASTRIC pH
8
7
6
5
4
3
2
1
3.0 ± 0.7
7.0 ± 0.6
6.8 ± 1.0
5.8 ± 1.9
PRE-SOS
2 HR p̄ 1ST DOSE
DAILY, PRE-DOSE (x̄)
THE LOWEST GASTRIC pH

FIG. 2

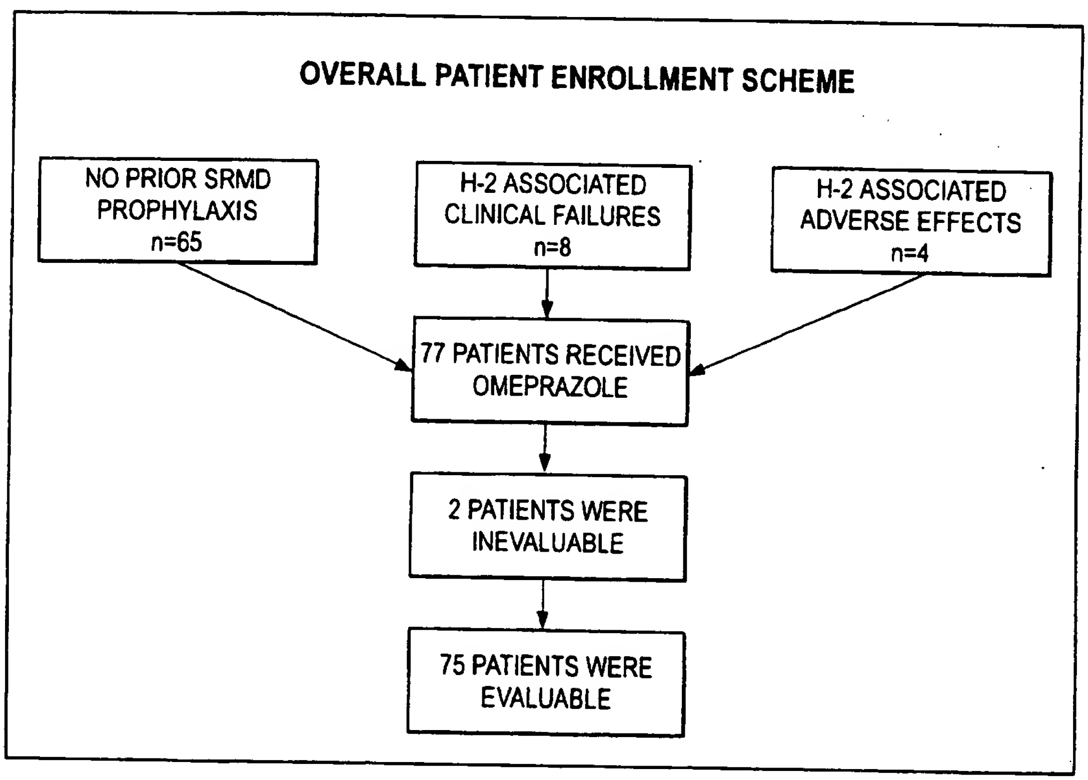

OVERALL PATIENT ENROLLMENT SCHEME
NO PRIOR SRMD PROPHYLAXIS n=65
H-2 ASSOCIATED CLINICAL FAILURES n=8
H-2 ASSOCIATED ADVERSE EFFECTS n=4
77 PATIENTS RECEIVED OMEPRAZOLE
2 PATIENTS WERE INEVALUABLE
75 PATIENTS WERE EVALUABLE

FIG. 3

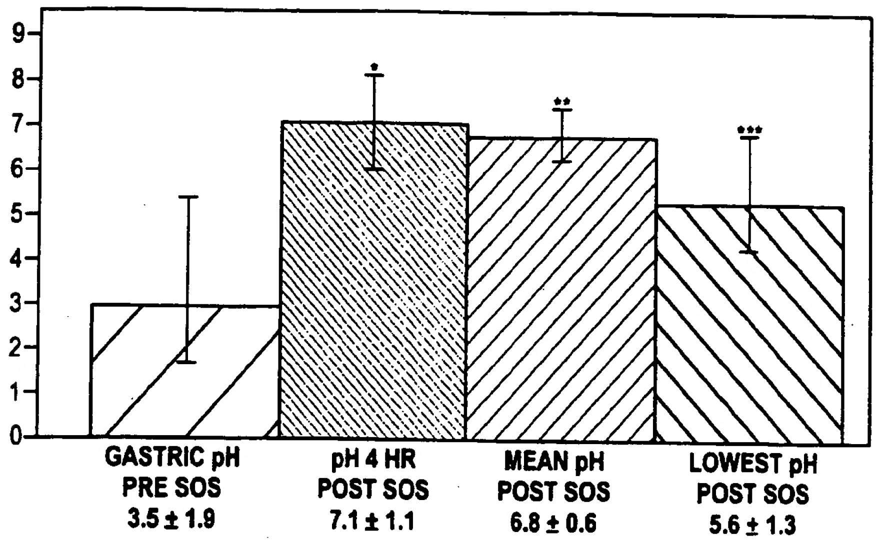
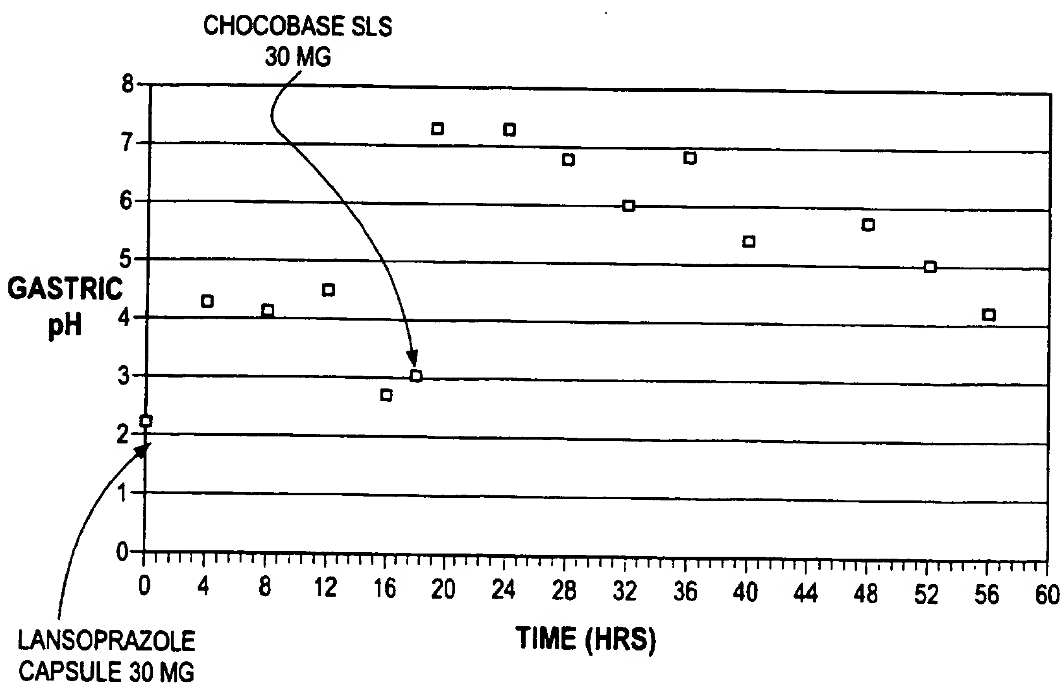

9
8
7
6
5
4
3
2
1
0
*
**
***
GASTRIC pH
PRE SOS
3.5 ± 1.9
pH 4 HR
POST SOS
7.1 ± 1.1
MEAN pH
POST SOS
6.8 ± 0.6
LOWEST pH
POST SOS
5.6 ± 1.3

FIG. 4


CHOCOBASE SLS
30 MG
GASTRIC
pH
8
7
6
5
4
3
2
1
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
TIME (HRS)
LANSOPRAZOLE
CAPSULE 30 MG

SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHOD OF USING SAME

This application is a continuation-in-part of U.S. patent application Ser. No. 09/183,422 filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/680,376 filed on Jul. 15, 1996, now U.S. Pat. No. 5,840,737, which claims priority to U.S. Provisional Application Serial No. 60/009,608 filed on Jan. 4, 1996. This application claims priority to all such previous applications, and such applications are hereby incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to pharmaceutical preparations comprising substituted benzimidazole proton pump inhibitors.

BACKGROUND OF THE INVENTION

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, that inhibits gastric acid secretion. Omeprazole belongs to a class of antisecretory compounds called proton pump inhibitors ("PPIs") that do not exhibit anticholinergic or H_2 histamine antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H^+, K^+-ATPase enzyme system (proton pump) at the secretory surface of the gastric parietal cell.

Typically, omeprazole, lansoprazole and other proton pump inhibitors are formulated in an enteric-coated solid dosage form (as either a delayed-release capsule or tablet) or as an intravenous solution (or as a product for reconstitution), and are prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. These above-listed conditions commonly arise in healthy or critically ill patients, and may be accompanied by significant upper gastrointestinal bleeding.

H_2-antagonists, antacids, and sucralfate are commonly administered to minimize the pain and the complications related to these conditions. These drugs have certain disadvantages associated with their use. Some of these drugs are not completely effective in the treatment of the aforementioned conditions and/or produce adverse side effects, such as mental confusion, constipation, diarrhea, and thrombocytopenia. H_2-antagonists, such as ranitidine and cimetidine, are relatively costly modes of therapy, particularly in NPO patients, which frequently require the use of automated infusion pumps for continuous intravenous infusion of the drug.

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, Pathogenesis, Diagnosis and Treatment of Acute Gastric Mucosa Lesions, Clin Gastroenterol 13: 635–650 (1984)). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., The Prevention of Gastrointestinal Tract Bleeding in Patients in an Intensive Care Unit, Surg. Gynecol. Obstet., 153: 214–220 (1981); Larson et al., Gastric Response to Severe Head Injury, Am. J. Surg. 147: 97–105 (1984); Czaja et al., Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History, N Engl. J. Med, 291: 925–929 (1974); Skillman et al., Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated with Lethal Hemorrhage From Acute Stress Ulceration, Am. J. Surg., 117: 523–530 (1969); and Cook et al., Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients, N. Engl. J. Med., 330:377–381 (1994)). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients, N. Engl. J. Med., 330:377–381 (1994)). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., Continuous Intravenous cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia, Crit. Care Med., 21: 19–39 ('1993)). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History, N Engl. J. Med, 291: 925–929 (1974); Peura and Johnson, Cimetidine for Prevention and Treatment of Gastroduodenal Mucosal Lesions in Patients in an Intensive Care Unit, Ann Intern Med., 103: 173–177 (1985)). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.

In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage and related complications is considered by many to be the standard of care (AMA Drug Evaluations). However, general consensus is lacking about which drugs to use in this setting (Martin et al., Continuous Intravenous Cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia, Crit. Care Med., 21: 19–39 (1993); Gafter et al., Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity with Cimetidine, Am. J. Gastroenterol, 64: 560–562 (1989) Martin et al., Stress Ulcers and Organ Failure in Intubated Patients in Surgical Intensive Care Units, Ann Surg., 215: 332–337 (1992)). In two recent meta-analyses (Cook et al., Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis, Am. J. Med., 91: 519–527 (1991); Tryba, Stress Ulcer Prophylaxis—Quo Vadis? Intens. Care Med. 20: 311–313 (1994)) Antacids, sucralfate, and H_2-antagonists were all found to be superior to placebo and similar to one another in preventing upper gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in fifteen to twenty percent of patients in which they are employed because of failure to prevent bleeding or control pH (Ostro et al., Control of Gastric pH With Cimetidire Boluses Versus Primed Infusions, Gastroenterology, 89: 532–537 (1985) Siepler, A Dosage Alternative for H-2 Receptor Antagonists, Continuous-Infusion, Clin. Ther., 8 (Suppl A): 24–33 (1986); Ballesteros et al., Bolus or Intravenous Infusion of Ranitidine: Effects on Gastric pH and Acid Secretion: A Comparison of Relative Cost and Efficacy, Ann. Intern. Med., 112:334–339 (1990)), or because of adverse effects (Gafter et al., Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity With Cimetidine, Am. J. Gastroenterol, 64: 560–562 (1989); Sax, Clinically Important Adverse Effects and Drug Interactions With H2-Receptor Antagonists: An Update, Pharmacotherapy 7(6 pt 2): 110S–115S (1987); Vial et al., Side Effects of Ranitidine, Drug Saf, 6:94–117(1991); Cantu and Korek,

Central Nervous System Reactions to Histamine-2 Receptor Blockers, Ann. Intern Med., 114: 1027–1034 (1991); and Spychal and Wickham, Thrombocytopenia Associated With Ranitidine, Br. Med. J., 291: 1687 (1985)). In addition, the characteristics of an ideal agent for the prophylaxis of stress gastritis were analyzed by Smythe and Zarowitz, Changing Perspectives of Stress Gastritis Prophylaxis, Ann Pharmacother, 28: 1073–1084 (1994) who concluded that none of the agents-currently in use fulfill their criteria.

Stress ulcer prophylaxis has become routine therapy in intensive care units in most hospitals (Fabian et al., Pneumonia and Stress Ulceration in Severely Injured Patients, Arch. Surg., 128: 185–191 (1993); Cook et al., Stress Ulcer Prophylaxis in the Critically Ill: A Meta-Analysis, Am. J. Med., 91: 519–527 (1991)). Controversy remains regarding pharmacologic intervention to prevent stress-related bleeding in critical care patients. It has been suggested that the incidence and risk of gastrointestinal bleeding has decreased in the last ten years and drug therapy may no longer be needed (Cook et al., Risk Factors for Gastrointestinal Bleeding in Critically Ill. Patients, N. Engl. J. Med., 330:377–381 (1994); Tryba, Stress Ulcer Prophylaxis—Quo Vadis? Intens. Care Med. 20: 311–313 (1994); Schepp, Stress Ulcer Prophylaxis.: Still a Valid Option in the 1990s?, Digestion 54: 189–199 (1993)). This reasoning is not supported by a recent placebo-controlled study. Martin. et al. conducted a prospective, randomized, double-blind, placebo-controlled comparison of continuous-infusion cimetidine and placebo for the prophylaxis of stress-related mucosal damage. The study was terminated early because of excessive bleeding-related mortality in the placebo group. It appears that the natural course of stress-related mucosal damage in a patient at risk who receives no prophylaxis remains significant. In the placebo group, thirty-three percent (33%) of patients developed clinically significant bleeding, nine percent (9%) required transfusion, and six percent (6%) died due to bleeding-related complications. In comparison, fourteen percent (14%) of cimetidine-treated patients developed clinically significant bleeding, six percent (6%) required transfusions, and one and one-half percent (1.5%) died due to bleeding-related complication. The difference in bleeding rates between treatment groups was statistically significant. This study clearly demonstrated that continuous-infusion cimetidine reduced morbidity in critical care patients. Although these data were used to support the approval of continuous-infusion cimetidine by the Food and Drug Administration for stress ulcer prophylaxis, H_2-antagonists fall short of being the optimal pharmacotherapeutic agents for preventing of stress-related mucosal bleeding.

Another controversy surrounding stress ulcer prophylaxis is which drug to use. In addition to the various H_2-antagonists, antacids and sucralfate are other treatment options for the prophylaxis of stress-related mucosal damage. An ideal drug in this setting should possess the following characteristics: prevent stress ulcers and their complications, be devoid of toxicity, lack drug interactions, be selective, have minimal associated costs (such as personnel time and materials), and be easy to administer (Smythe and Zarowitz, Changing Perspectives of Stress Gastritis Prophylaxis, Ann Pharmacother, 28: 1073–1084 (1994)). Some have suggested that sucralfate is possibly the ideal agent for stress ulcer prophylaxis (Smythe and Zarowitz, Changing Perspectives of Stress Gastritis Prophylaxis, Ann Pharmacother, 28: 1073–1084 (1994)). Randomized, controlled studies support the use of sucralfate (Borrero et al., Antacids vs. Sucralfate in Preventing Acute Gastrointestinal Tract Bleeding in Abdominal Aortic Augery, Arch. Surg., 121: 810–812 (1986); Tryba, Risk of Acute Stress Bleeding and Nosocomial Pneumonia in Ventilated Intensive Care Patients. Sucralfate vs. Antacids, Am. J. Med., 87(3B): 117–124 (1987); Cioffi et al., Comparison of Acid Neutralizing and Non-acid Neutralizing Stress Ulcer Prophylaxis in Thermally Injured Patients. J. Trauma, 36: 541–547 (1994); and Driks et al., Nosocomial Pneumonia in Intubated Patients Given Sucralfate as Compared With Antacids or Histamine Type 2 Blockers, N. Engl. J. Med., 317: 1376–1382 1987)), but data on critical care patients with head injury, trauma, or burns are limited. In addition, a recent study comparing sucralfate and cimetidine plus antacids for stress ulcer prophylaxis reported clinically significant bleeding in three of forty-eight (6%) sucralfate-treated patients, one of whom required a gastrectomy (Cioffi et al., Comparison of Acid Neutralizing and Non-acid Neutralizing Stress Ulcer Prophylaxis in Thermally Injured Patients, J. Trauma, 36: 541–547 (1994)). In the study performed by Driks and coworkers that compared sucralfate to conventional therapy (H_2-antagonists, antacids, or H_2-antagonists plus antacids), the only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm (Driks et al., Nosocomial Pneumonia in Intubated Patients Given Sucralfate as Compared With Antacids or Histamine Type 2 Blockers, N. Engl. J. Med., 317: 1376–1382(1987)).

H_2-antagonists fulfill many of the criteria for an ideal stress ulcer prophylaxis drug. Yet, clinically significant bleeds can occur during. H_2-antagonist prophylaxis (Martin et al., Continuous Intravenous Cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia, Crit. Care Med., 21: 19–39 (1993); Cook et al. , Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis, Am. J. Med., 91: 519–527 (1991); Schuman et al., Prophylactic Therapy for Acute Ulcer Bleeding: A Reappraisal, Ann Intern. Med, 106: 562–567 (1987)). Adverse events are not uncommon in the critical care population (Gafter et al., Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-Reactivity With Cimetidine, Am. J. Gastroenterol, 64: 560–562 (1989); Sax, Clinically Important Adverse Effects and Drug Interactions With H2-receptor Antagonists: An Update, Pharmacotherapy 7(6 pt 2): 110S–115S (1987); Vial et al., Side Effects of Ranitidine, Drug Saf., 6:94–117(1991); Cantu and Korek, Central Nervous System Reactions to Histamine-2 Receptor Blockers, Ann. Intern Med., 114: 1027–1034 (1991); Spychal and Wickham, Thrombocytopenia Associated With Ranitidine, Br. Med. J., 291: 1687 (1985)).

One reason proposed for the therapeutic H_2-antagonist failures is lack of pH control throughout the treatment period (Ostro et al., Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions, Gastroenterology, 89: 532–537 (1985)). Although the precise pathophysiologic mechanisms involved in stress ulceration are not clearly established, the high concentration of hydrogen ions in the mucosa (Fiddian-Green et al., 1987) or gastric fluid in contact with mucosal cells appears to be an important factor. A gastric pH >3.5 has been associated with a lower incidence of stress-related mucosal damage and bleeding (Larson et al., Gastric Response to Severe Head Injury, Am. J. Surg. 147: 97–105 (1984); Skillman et al., Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated With Lethal Hemorrhage From Acute Stress Ulceration, Am. J. Surg., 117: 523–530 (1969); Skillman et al., The Gastric Mucosal Barrier: Clinical and Experimental Studies in Critically Ill and Normal Man and in the Rabbit, Ann Surg., 172: 564–584 (1970); and Priebe and Skillman, Methods of Prophylaxis in Stress Ulcer Disease, World J. Surg., 5: 223–233 (1981)). Several studies have shown that H_2-antagonists, even in maximal doses, do not reliably or continuously increase intragastric pH above commonly targeted levels (3.5 to 4.5). This is true especially when used in fixed-dose bolus regimens (Ostro et al., Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions,

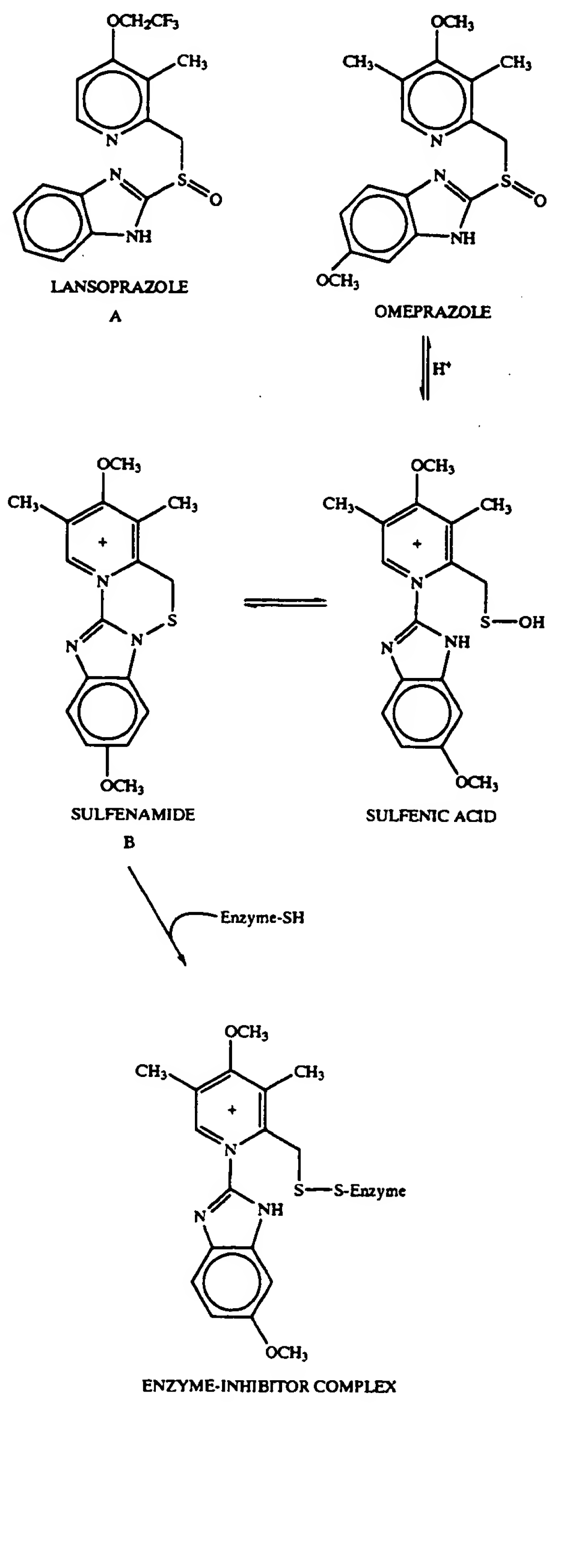
Gastroenterology, 89: 532–537 (1985); Siepler, A Dosage Alternative for H-2 Receptor Antagonists, Continuous-infusion, Clin. Ther., 8 (Suppl A): 24–33 (1986); Ballesteros et al., Bolus or Intravenous Infusion of Ranitidine: Effects on Gastric pH and Acid Secretion: A Comparison of Relative Cost and Efficacy, Ann. Intern. Med., 112:334–339 (1990)). In addition, gastric pH levels tend to trend downward with time when using a continuous-infusion of H_2-antagonists, which may be the result of tachyphylaxis (Ostro et al., Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions, Gastroenterology, 89: 532–537 (1985); Wilder-Smith and Merki, Tolerance During Dosing With H_2-receptor Antagonists. An Overview, Scand. J. Gastroenterol 27 (suppl. 193): 14–19 (1992)).

Because stress ulcer prophylaxis is frequently employed in the intensive care unit, it is essential from both a clinical and economic standpoint to optimize the pharmacotherapeutic approach. In an attempt to identify optimal therapy, cost of care becomes an issue. All treatment costs should be considered, including the costs of treatment failures and drug-related adverse events. While the actual number of failures resulting in mortality is low, morbidity (e.g., bleeding that requires blood transfusion) can be high, even though its association with the failure of a specific drug is often unrecognized.

Initial reports of increased frequency of pneumonia in patients receiving stress ulcer prophylaxis with agents that raise gastric pH has influenced the pharmacotherapeutic approach to management of critical care patients. However, several recent studies (Simms et al., Role of Gastric Colonization in the Development of Pneumonia in Critically Ill Trauma Patients: Results of a Prospective Randomized Trial, J. Trauma, 31: 531–536 (1991); Pickworth et al., Occurrence of Nasocomial Pneumonia in Mechanically Ventilated Trauma Patients: A Comparison of Sucralfate and Ranitidine, Crit. Care Med., 12: 1856–1862 (1993); Ryan et al., Nasocomial Pneumonia During Stress Ulcer Prophylaxis With Cimetidine and Sucralfate, Arch. Surg., 128: 1353–1357 (1993); Fabian et al., Pneumonia and Stress Ulceration in Severely Injured Patients, Arch. Surg., 128: 185–191 (1993)), a meta-analysis (Cook et al., Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis, Am. J. Med., 91: 519–527 (1991)), and a closer examination of the studies that initiated the elevated pH-associated pneumonia hypotheses (Schepp, Stress Ulcer Prophylaxis: Still a Valid Option in the 1990s?, Digestion 54: 189–199 (1993)) cast doubt on a causal relationship. The relationship between pneumonia and antacid therapy is much stronger than for H_2-antagonists. The shared effect of antacids and H_2-antagonists on gastric pH seems an irresistible common cause explanation for nosocomial pneumonia observed during stress ulcer prophylaxis. However, there are important differences between these agents that are not often emphasized (Laggner et al., Prevention of Upper Gastrointestinal Bleeding in Long-term Ventilated Patients, Am. J. Med., 86 (suppl 6A) : 81–84 (1989)). When antacids are exclusively used to control pH in the prophylaxis of stress-related upper gastrointestinal bleeding, large volumes are needed. Volume, with or without subsequent reflux, may be the underlying mechanism(s) promoting the development of pneumonia in susceptible patient populations rather than the increased gastric pH. The rate of pneumonia (12%) was not unexpected in this critical care population and compares with sucralfate, which does not significantly raise gastric pH (Pickworth et al., Occurrence of Nasocomial Pneumonia in Mechanically Ventilated Trauma Patients: A Comparison of Sucralfate and Ranitidine, Crit. Care Med., 12: 1856–1862 (1993); Ryan et al., Nasocomial Pneumonia During Stress Ulcer Prophylaxis With Cimetidine and Sucralfate, Arch. Surg., 128: 1353–1357 (1993)).

Omeprazole (Prilosec®), lansoprazole (Prevacid®) and other PPIs reduce gastric acid production by inhibiting H^+,K^+-ATPase of the parietal cell-the final common pathway for gastric acid secretion (Fellenius et al., Substituted Benzimidazoles Inhibit Gastric Acid Secretion by Blocking H^+,K^+-ATPase, Nature, 290: 159–161 (1981); Wallmark et al, The Relationship Between Gastric Acid Secretion and Gastric H^+,K^+-ATPase Activity, J. Biol. Chem., 260: 13681–13684 (1985); Fryklund et al., Function and Structure of Parietal Cells After H^+,K^+-ATPase Blockade, Am. J. Physiol., 254 (3 pt 1) ; G399–407 (1988)).

PPIs contain a sulfinyl group in a bridge between substituted benzimidazole and pyridine rings, as illustrated below.



At neutral pH, omeprazole, lansoprazole and other PPIs are chemically stable, lipid-soluble, weak bases that are devoid of inhibitory activity. These neutral weak bases reach parietal cells from the blood and diffuse into the secretory canaliculi, where the drugs become protonated and thereby trapped. The protonated agent rearranges to form a sulfenic acid and a sulfenamide. The sulfenamide interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane-spanning H^+,K^+-ATPase (Hardman et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, p. 907 (9th ed. 1996)). Omeprazole and lansoprazole, therefore, are prodrugs that must be activated to be effective. The specificity of the effects of PPIs is also dependent upon: (a) the selective distribution of H^+,K^+-ATPase; (b) the requirement for acidic conditions to catalyze generation of the reactive inhibitor; and (c) the trapping of the protonated drug and the cationic sulfenamide within the acidic canaliculi and adjacent to the target enzyme. (Hardman et al., 1996)).

Omeprazole and lansoprazole are available for oral administration as enteric coated particles in gelatin capsules. Other proton pump inhibitors such as rabeprazole and pantoprazole are supplied as enteric coated tablets. The enteric dosage forms of the prior art have been employed because it is very important that these drugs not be exposed to gastric acid prior to absorption. Although these drugs are stable at alkaline pH, they are destroyed rapidly as pH falls (e.g., by gastric acid). Therefore, if the microencapsulation or the enteric coating is disrupted (e.g., trituration to compound a liquid, or chewing the capsule), the drug will be exposed to degradation by the gastric acid in the stomach.

The absence of an intravenous or oral liquid dosage form in the United-States has limited the testing and use of omeprazole, lansoprazole and rabeprazole in the critical care patient population. Barie et al., Therapeutic Use of Omeprazole for Refractory Stress-induced Gastric Mucosal Hemorrhage, Crit. Care Med., 20: 899–901 (1992) have described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multiorgan failure. However, such pellets are not ideal as they can aggregate and occlude such tubes, and they are not suitable for patients who cannot swallow the pellets. Am J. Health-Syst Pharm 56:2327–30 (1999).

Proton pump inhibitors such as omeprazole represent an advantageous alternative to the use of H_2-antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage. However, in their current form (capsules containing enteric-coated granules or enteric-coated tablets), proton pump inhibitors can be difficult or impossible to administer to patients who are either unwilling or unable to swallow tablets or capsules, such as critically ill patients, children, the elderly, and patients suffering from dysphagia. Therefore, it would be desirable to formulate a proton pump inhibitor solution or suspension which can be enterally delivered to a patient thereby providing the benefits of the proton pump inhibitor without the drawbacks of the current enteric-coated solid dosage forms.

Omeprazole, the first proton pump inhibitor introduced into use, has been formulated in many different embodiments such as in a mixture of polyethylene glycols, adeps solidus and sodium lauryl sulfate in a soluble, basic amino acid to yield a formulation designed for administration in the rectum as taught by U.S. Pat. No. 5,219,870 to Kim.

U.S. Pat. No. 5,395,323 to Berglund ('323) discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient. The '323 patent teaches the use of an omeprazole tablet which is placed in the device and dissolved by normal saline, and infused parenterally into the patient. This device and method of parenteral infusion of omeprazole does not provide the omeprazole solution as an enteral product, nor is this omeprazole solution directly administered to the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate antacid effect of the present formulation..

U.S. Pat. No. 4,786,505 to Lovgren et al. discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH. The powder mixture is then formulated to small beads, pellets, tablets and may be loaded into capsules by conventional pharmaceutical procedures. This formulation of omeprazole does not provide an omeprazole dosage form which can be enterally administered to a patient who may be unable and/or unwilling to swallow capsules, tablets or pellets, nor does it teach a convenient form which can be used to make an omeprazole or other proton pump inhibitor solution or suspension.

Several buffered omeprazole oral solutions/suspensions have been disclosed. For example, Pilbrant et al., Development of an Oral Formulation of Omeprazole, Scand. J. Gastroent. 20 (Suppl. 108): 113–120 (1985) teaches the use of micronized omeprazole suspended in water, methylcellulose and sodium bicarbonate in a concentration of approximately 1.2 mg omeprazole/ml suspension.

Andersson et el., Pharmacokinetics of Various Single Intravenous and Oral Doses of Omeprazole, Eur J. Clin. Pharmacol. 39:, 195–197 (1990) discloses 10 mg, 40 mg, and 90 mg of oral omeprazole dissolved in PEG 400, sodium bicarbonate and water. The concentration of omeprazole cannot be determined as volumes of diluent are not disclosed. Nevertheless, it is apparent from this reference that multiple doses of sodium bicarbonate were administered with and after the omeprazole suspension.

Andersson et al., Pharmacokinetics and Bioavailability of Omeprazole After Single and Repeated Oral Administration in Healthy Subjects, Br. J. Clin. Pharmac. 29: 557–63 (1990) teaches the oral use of 20 mg of omeprazole, which was dissolved in 20 g of PEG 400 (sp. gravity=1.14) and diluted with 50 ml of sodium bicarbonate, resulting in a concentration of 0.3 mg/ml.

Regardh et al., The Pharmacokinetics of Omeprazole in Humans—A Study of Single Intravenous and Oral Doses, Ther. Drug Mon. 12: 163–72 (1990) discloses an oral dose of omeprazole at a concentration 0.4 mg/ml after the drug was dissolved in PEG 400, water and sodium bicarbonate.

Landahl et al., Pharmacokinetics Study of Omeprazole in Elderly Healthy Volunteeers, Clin. Pharmacokinetics 23 (6): 469–476 (1992) teaches the use of an oral dose of 40 mg of omeprazole dissolved in PEG 400, sodium bicarbonate and water. This reference does not disclose the final concentrations utilized. Again, this reference teaches the multiple administration of sodium bicarbonate after the omeprazole solution.

Andersson et al., Pharmacokinetics of [^{14}C] Omeprazole in Patients with Liver Cirrhosis, Clin. Pharmacokinetics 24(1): 71–78 (1993) discloses the oral administration of 40 mg of omeprazole which was dissolved in PEG 400, water and sodium bicarbonate. This reference does not teach the final concentration of the omeprazole solution administered, although it emphasizes the need for concomitant sodium bicarbonate dosing to prevent acid degradation of the drug.

Nakagawa, et al., Lansoprazole: Phase I Study of lansoprazole (AG-1749) Anti-ulcer Agent, J. Clin. Therapeutics & Med. (1991) teaches the oral administration of 30 mg of lansoprazole suspended in 100 ml of sodium bicarbonate (0.3 mg/ml), which was administered to patients through a nasogastric tube.

All of the buffered omeprazole solutions described in these references were administered orally, and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration. In all of these studies, repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration. In the above-cited studies, as much as 48 mmoles of sodium bicarbonate in 300 ml of water must be ingested for a single dose of omeprazole to be orally administered.

The buffered omeprazole solutions of the above cited prior art require the ingestion of large amounts of sodium bicarbonate and large volumes of water by repeated administration. This has been considered necessary to prevent acid degradation of the omeprazole. In the above-cited studies, basically healthy volunteers, rather than sick patients, were given dilute buffered omeprazole utilizing pre-dosing and post-dosing with large volumes of sodium bicarbonate.

The administration of large amounts of sodium bicarbonate can produce at least six significant adverse effects, which can dramatically reduce the efficacy of the omeprazole in patients and reduce the overall health of the patients. First, the fluid volumes of these dosing protocols would not be suitable for sick or critically ill patients who must receive multiple doses of omeprazole. The large volumes would result in the distention of the stomach and increase the likelihood of complications in critically ill patients such as the aspiration of gastric contents.

Second, because bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their reflux disease as the belching can cause upward movement of stomach acid (Brunton, Agents for the Control of Gastric Acidity and Treatment of Peptic Ulcers, In, Goodman A G, et al. The Pharmacologic Basis of Therapeutics (New York, p. 907 (1990)).

Third, patients with conditions such as hypertension or heart failure are standardly advised to avoid the intake of excessive sodium as it can cause aggravation or exacerbation of their hypertensive conditions (Brunton, supra). The ingestion of large amounts of sodium bicarbonate is inconsistent with this advice.

Fourth, patients with numerous conditions that typically accompany critical illness should avoid the intake of excessive sodium bicarbonate as it can cause metabolic alkalosis that can result in a serious worsening of the patient's condition.

Fifth, excessive antacid intake (such as sodium bicarbonate) can result in drug interactions that produce serious adverse effects. For example, by altering gastric and urinary pH, antacids can alter rates of drug dissolution and absorption, bioavailability, and renal elimination (Brunton, supra).

Sixth, because the buffered omeprazole solutions of the prior art require prolonged administration of sodium bicarbonate, it makes it difficult for patients to comply with the regimens of the prior art. For example, Pilbrant. et al. disclose an oral omeprazole administration protocol calling for the administration to a subject who has been fasting for at least ten hours, a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later, the subject ingests a suspension of 60 mg of omeprazole in 50 ml of water that also contains 8 mmoles of sodium bicarbonate. This is rinsed down with another 50 ml of 8 mmoles sodium bicarbonate solution. Ten minutes after the ingestion of the omeprazole dose, the subject ingests 50 ml of bicarbonate solution (8 mmoles). This is repeated at twenty minutes and thirty minutes post omeprazole dosing to yield a total of 48 mmoles of, sodium bicarbonate and 300 ml of water in total which are ingested by the subject for a single omeprazole dose. Not only does this regimen require the ingestion of excessive amounts of bicarbonate and water, which is likely to be dangerous to some patients, it is unlikely that even healthy patients would comply with this regimen.

It is well documented that patients who are required to follow complex schedules for drug administration are non-compliant and, thus, the efficacy of the buffered omeprazole solutions of the prior art would be expected to be reduced due to non-compliance. Compliance has been found to be markedly reduced when patients are required to deviate from a schedule of one or two (usually morning and night) doses of a medication per day. The use of the prior art buffered omeprazole solutions which require administration protocols with numerous steps, different drugs (sodium bicarbonate+omeprazole+PEG 400 versus sodium bicarbonate alone), and specific time allotments between each stage of the total omeprazole regimen in order to achieve efficacious results is clearly in contrast with both current drug compliance theories and human nature.

The prior art (Pilbrant et al., 1985) teaches that the buffered omeprazole suspension can be stored at refrigerator temperatures for a week and deep frozen for a year while still maintaining 99% of its initial potency. It would be desirable to have an omeprazole or other proton pump inhibitor solution or suspension that could be stored at room temperature or in a refrigerator, for periods of time which exceed those of the prior art while still maintaining 99% of the initial potency. Additionally, it would be advantageous to have a form of the omeprazole and bicarbonate which can be utilized to instantly make the omeprazole solution/suspension of the present invention which is supplied in a solid form which imparts the advantages of improved shelf-life at room temperature, lower cost to produce, less expensive shipping costs, and which is less expensive to store.

It would, therefore, be desirable to have a proton pump inhibitor formulation, which provides a cost-effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonists, antacids, and sucralfate. Further, it would be desirable to have a proton pump inhibitor formulation which is convenient to prepare and administer to patients unable to ingest solid dosage forms such as tablets or capsules, which is rapidly absorbed, and can be orally or enterally delivered as a liquid form or solid form. It is desirable that the liquid formulation not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an antacid immediately upon delivery.

It would further be advantageous to have a potentiator or enhancer of the pharmacological activity of the PPIs. It has been theorized by applicant that the PPIs can only exert their effects on H^+,K^+-ATPase when the parietal cells are active. Accordingly, applicant has identified, as discussed below, parietal cell activators that are administered to synergistically enhance the activity of the PPIs.

Additionally, the intravenous dosage forms of PPIs of the prior art are often administered in larger doses than the oral forms. For example, the typical adult IV dose of omeprazole is greater than 100 mg/day whereas the adult oral dose is 20 to 40 mg/day. Large IV doses are necessary to achieve the

desired pharmacologic effect because, it is believed, many of the parietal cells are in a resting phase (mostly inactive) during an IV dose given to patients who are not taking oral substances by mouth (npo) and, therefore, there is little active (that which is inserted into the secretory canalicular membrane) H^+,K^+-ATPase to inhibit. Because of the clear disparity in the amount of drug necessary for IV versus oral doses, it would be very advantageous to have compositions and methods for IV administration where significantly less drug is required.

SUMMARY OF THE INVENTION AND ADVANTAGES

The foregoing advantages and objects are accomplished by the present invention. The present invention provides an oral solution/suspension comprising a proton pump inhibitor and at least one buffering agent. The PPI can be any substituted benzimidazole compound having H^+,K^+-ATPase inhibiting activity and being unstable to acid. Omeprazole and lansoprazole are the preferred PPIs for use in oral suspensions in concentrations of at least 1.2 mg/ml and 0.3 mg/ml, respectively. The liquid oral compositions can be further comprised of parietal cell activators, anti-foaming agents and/or flavoring agents.

The inventive composition can alternatively be formulated as a powder, tablet, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets and granules. Such dosage forms are advantageously devoid of any enteric coating or delayed or sustained-release delivery mechanisms, and comprise a PPI and at least one buffering agent to protect the PPI against acid degradation. Similar to the liquid dosage form, the dry forms can further include anti-foaming agents, parietal cell activators and flavoring agents.

Kits utilizing the inventive dry dosage forms are also disclosed herein to provide for the easy preparation of a liquid composition from the dry forms.

In accordance with the present invention, there is further provided a method of treating gastric acid disorders by administering to a patient a pharmaceutical composition comprising a proton pump inhibitor in a pharmaceutically acceptable carrier and at least one buffering agent wherein the administering step comprises providing a patient with a single dose of the composition without requiring further administering of the buffering agent.

Additionally, the present invention relates to a method for enhancing the pharmacological activity of an intravenously administered proton pump inhibitor in which at least one parietal cell activator is orally administered to the patient before, during and/or after the intravenous administrations of the proton pump inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

FIG. 1 is a graph showing the effect of the omeprazole solution of the present invention on gastric pH in patients at risk for upper gastrointestinal bleeding from stress-related mucosal damage;

FIG. 2 is a flow chart illustrating a patient enrollment scheme;

FIG. 3 is a bar graph illustrating gastric pH both pre- and post-administration of omeprazole solution according to the present invention; and

FIG. 4 is a graph illustrating the stomach pH values after the oral administration of both chocolate plus lansoprazole and lansoprazole alone.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention relates to a pharmaceutical composition comprising a proton pump inhibitor and a buffering agent with or without one or more parietal cell activators. While the present invention may be embodied in many different forms, several specific embodiments are discussed herein with the understanding that the present disclosure is to be considered only as an exemplification of the principles of the invention, and it is not intended to limit the invention to the embodiments illustrated.

For the purposes of this application, the term "proton pump inhibitor" (PPI) shall mean any substituted benzimidazole possessing pharmacological activity as an inhibitor of H^+,K^+-ATPase, including, but not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, perprazole (s-omeprazole magnesium), habeprazole, ransoprazole, pariprazole, and leminoprazole in neutral form or a salt form, a single enantiomer or isomer or other derivative or an alkaline salt of an enantiomer of the same.

The inventive composition comprises dry formulations, solutions and/or suspensions of the proton pump inhibitors. As used herein, the terms "suspension" and "solution" are interchangeable with each other and mean solutions and/or suspensions of the substituted benzimidazoles.

After absorption of the PPI (or administration intravenously) the drug is delivered via the bloodstream to various tissues and cells of the body including the parietal cells. Research suggests that the PPI is in the form of a weak base and is non-ionized and thereby freely passes through physiologic membranes, including the cellular membranes of the parietal cell. It is believed that the non-ionized PPI moves into the acid-secreting portion of the parietal cell, the secretory canaliculus. Once in the acidic millieu of the secretory canaliculus, the PPI is apparently protonated (ionized) and converted to the active form of the drug. Generally, ionized proton pump inhibitors are membrane impermeable and form disulfide covalent bonds with cysteine residues in the alpha subunit of the proton pump.

The inventive pharmaceutical composition comprising a proton pump inhibitor such as omeprazole, lansoprazole or other proton pump inhibitor and derivatives thereof can be used for the treatment or prevention of gastrointestinal conditions including, but not limited to, active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison Syndrome. Treatment of these conditions is accomplished by administering to a patient an effective amount of the pharmaceutical composition according to the present invention.

The proton pump inhibitor is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. The term "effective amount" means, consistent with considerations known in the art, the amount of PPI or other agent effective to achieve a pharmacologic effect or therapeutic improvement without undue adverse side effects, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood transfusion, improved survival rate, more rapid recovery, parietal cell activation and H^+,K^+-ATPase inhibition or improvement or elimination of symptoms, and other indicators as are selected as appropriate measures by those skilled in the art.

The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range from approximately <2 mg/day to

approximately 300 mg/day. The standard approximate daily oral dosage is typically 20 mg of omeprazole, 30 mg lansoprazole, 40 mg pantoprazole, 20 mg rabeprazole, and the pharmacologically equivalent doses of the following PPIs: habeprazole, pariprazole, dontoprazole, ransoprazole, perprazole (s-omeprazole magnesium), and leminoprazole.

A pharmaceutical formulation of the proton pump inhibitors utilized in the present invention can be administered orally or enterally to the patient. This can be accomplished, for example, by administering the solution via a nasogastric (ng) tube or other indwelling tubes placed in the GI tract. In order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the PPI solution of the present invention is administered in a single dose which does not require any further administration of bicarbonate, or large amounts of bicarbonate, or other buffer following the administration of the PPI solution, nor does it require a large amount of bicarbonate or buffer in total. That is, unlike the prior art PPI solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose which does not require administration of bicarbonate either before or after administration of the PPI. The present invention eliminates the need to pre-or post-dose with additional volumes of water and sodium bicarbonate. The amount of bicarbonate administered via the single dose administration of the present invention is less than the amount of bicarbonate administered as taught in the prior art references cited above.

Preparation of Oral Liquids

The liquid oral pharmaceutical composition of the present invention is prepared by mixing omeprazole (Prilosec® AstraZeneca) or other proton pump inhibitor or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). Preferably, omeprazole or other proton pump inhibitor, which can be obtained from a capsule or tablet or obtained from the solution for parenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other PPI) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0 mg/ml. The preferred concentration for the omeprazole in the solution ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml, with 2.0 mg/ml being the standard concentration. For lansoprazole (Prevacid® TAP Pharmaceuticals, Inc.) the concentration can range from about 0.3 mg/ml to 10 mg/ml with the preferred concentration being about 3 mg/ml.

Although sodium bicarbonate is the preferred buffering agent employed in the present invention to protect the PPI against acid degradation, many other weak and strong bases (and mixtures thereof) can be utilized. For the purposes of this application, "buffering agent" shall mean any pharmaceutically appropriate weak base or strong base (and mixtures thereof) that, when formulated or delivered with (e.g., before, during and/or after) the PPI, functions to substantially prevent or inhibit the acid degradation of the PPI by gastric acid sufficient to preserve the bioavailability of the PPI administered. The buffering agent is administered in an amount sufficient to substantially achieve the above functionality. Therefore, the buffering agent of the present invention, when in the presence of gastric acid, must only elevate the pH of the stomach sufficiently to achieve adequate bioavailability of the drug to effect therapeutic action.

Accordingly, examples of buffering agents include, but are not limited to, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate coprecipitate, a mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium cholride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts.

The pharmaceutically acceptable carrier of the oral liquid preferably comprises a bicarbonate salt of Group IA metal as buffering agent, and can be prepared by mixing the bicarbonate salt of the Group IA metal, preferably sodium bicarbonate, with water. The concentration of the bicarbonate salt of the Group IA metal in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt of the Group IA metal ranges from approximately 7.5 percent to approximately 10.0 percent. In a preferred embodiment of the present invention, sodium bicarbonate is the preferred salt and is present in a concentration of approximately 8.4 percent.

More specifically, the amount of sodium bicarbonate 8.4% used in the solution of the present invention is approximately 1 mEq (or mmole) sodium bicarbonate per 2 mg omeprazole, with a range of approximately 0.2 mEq (mmole) to 5 mEq (mmole) per 2 mg of omeprazole.

In a preferred embodiment of the present invention, enterically-coated omeprazole particles are obtained from delayed release capsules (Prilosec® AstraZeneca). Alternatively, omeprazole powder can be used. The enterically coated omeprazole particles are mixed with a sodium bicarbonate ($NaHCO_3$) solution (8.4%), which dissolves the enteric coating and forms an omeprazole solution. The omeprazole solution has pharmacokinetic advantages over standard time-released omeprazole capsules, including: (a) more rapid drug absorbance time (about 10 to 60 minutes) following administration for the omeprazole solution versus about 1 to 3 hours following administration for the enteric-coated pellets; (b) the $NaHCO_3$ solution protects the omeprazole from acid degradation prior to absorption; (c) the $NaHCO_3$ acts as an antacid while the omeprazole is being absorbed; and (d) the solution can be administered through an existing indwelling tube without clogging, for example, nasogastric or other feeding tubes (jejunal or duodenal), including small bore needle catheter feeding tubes.

Additionally, various additives can be incorporated into the inventive solution to enhance its stability, sterility and isotonicity. Further, antimicrobial preservatives, antioxidants, chelating agents, and additional buffers can be added, such as ambicin. However, microbiological evidence shows that this formulation inherently possesses antimicrobial and antifungal activity. Various antibacterial and antifungal agents such as, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like can enhance prevention of the action of microorganisms.

In many cases, it would be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Additionally, thickening agents such as methylcellulose are desirable to use in order to reduce the settling of the omeprazole or other PPI or derivatives thereof from the suspension.

The liquid oral solution may further comprise flavoring agents (e.g., chocolate, root beer or watermelon) or other flavorings stable at pH 7 to 9, anti-foaming agents (e.g.,

simethicone 80 mg, Mylicon®) and parietal cell activators (discussed below).

The present invention further includes a pharmaceutical composition comprising omeprazole or other proton pump inhibitor and derivatives thereof and at least one buffering agent in a form convenient for storage, whereby when the composition is placed into an aqueous solution, the composition dissolves yielding a suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution or suspension in an aqueous solution. The omeprazole or other PPIs and buffering agent can be formed into a tablet, capsule, pellets or granules, by methods well known to those skilled in the art.

The resultant omeprazole solution is stable at room temperature for several weeks and inhibits the growth of bacteria or fungi as shown in Example X below. Indeed, as established in Example XIII, the solution maintains greater than 90% of its potency for 12 months. By providing a pharmaceutical composition including omeprazole or other PPI with buffer in a solid form, which can be later dissolved or suspended in a prescribed amount of aqueous solution to yield the desired concentration of omeprazole and buffer, the cost of production, shipping, and storage are greatly reduced as no liquids are shipped (reducing weight and cost), and there is no need to refrigerate the solid form of the composition or the solution. Once mixed the resultant solution can then be used to provide dosages for a single patient over a course of time, or for several patients.

Tablets and Other Solid Dosage Forms

As mentioned above, the formulations of the present invention can also be manufactured in concentrated forms, such as tablets, suspension tablets and effervescent tablets or powders, such that upon reaction with water or other diluent, the aqueous form of the present invention is produced for oral, enteral or parenteral administration.

The present pharmaceutical tablets or other solid dosage forms disintegrate rapidly in aqueous media and form an aqueous solution of the PPI and buffering agent with minimal shaking or agitation. Such tablets utilize commonly available materials and achieve these and other desirable objectives. The tablets or other solid dosage forms of this invention provide for precise dosing of a PPI that may be of low solubility in water. They are particularly useful for medicating children and the elderly and others in a way that is much more acceptable than swallowing or chewing a tablet. The tablets that are produced have low friability, making them easily transportable.

The term "suspension tablets" as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the PPI. The suspension tablets of this invention comprise, in combination, a therapeutic amount of a PPI, a buffering agent, and a disintegrant. More particularly, the suspension tablets comprise about 20 mg omeprazole and about 1–20 mEq of sodium bicarbonate.

Croscarmellose sodium is a known disintegrant for tablet formulations, and is available from FMC Corporation, Philadelphia, Pa. under the trademark Ac-Di-Sol®. It is frequently blended in compressed tableting formulations either alone or in combination with microcrystalline cellulose to achieve rapid disintegration of the tablet.

Microcrystalline cellulose, alone or coprocessed with other ingredients, is also a common additive for compressed tablets and is well known for its ability to improve compressibility of difficult to compress tablet materials. It is commercially available under the Avicel® trademark. Two different Avicel® products are utilized, Avicel® PH which is microcrystalline cellulose, and Avicel® AC-815, a coprocessed spray dried residue of microcrystalline cellulose and a calcium, sodium alginate complex in which the calcium to sodium ratio is in the range of about 0.40:1 to about 2.5:1. While AC-815 is comprised of 85% microcrystalline cellulose (MCC) and 15% of a calcium, sodium alginate complex, for purposes of the present invention this ratio may be varied from about 75% MCC to 25% alginate up to about 95% MCC to 5% alginate. Depending on the particular formulation and active ingredient, these two components may be present in approximately equal amounts or in unequal amounts, and either may comprise from about 10% to about 50% by weight of the tablet.

The suspension tablet composition may, in addition to the ingredients described above, contain other ingredients often used in pharmaceutical tablets, including flavoring agents, sweetening agents, flow aids, lubricants or other common tablet adjuvants, as will be apparent to those skilled in the art. Other disintegrants, such as crospbvidone and sodium starch glycolate may be employed, although croscarmellose sodium is preferred.

In addition to the suspension tablet, the solid formulation of the present invention can be in the form of a powder, a tablet, a capsule, or other suitable solid dosage form (e.g., a pelleted form or an effervescing tablet, troche or powder), which creates the inventive solution in the presence of diluent or upon ingestion. For example, the water in the stomach secretions or water which is used to swallow the solid dosage form can serve as the aqueous diluent.

Compressed tablets are solid dosage forms prepared by compacting a formulation containing an active ingredient and excipients selected to aid the processing and improve the properties of the product. The term "compressed tablet" generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression or by pre-compaction tapping followed by a final compression.

Such solid forms can be manufactured as is well known in the art. Tablet forms can include, for example, one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmaceutically compatible carriers. The manufacturing processes may employ one, or a combination of, four established methods: (1) dry mixing; (2) direct compression; (3) milling; and (4) non-aqueous granulation. Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Such tablets may also comprise film coatings, which preferably dissolve upon oral ingestion or upon contact with diluent.

Non-limiting examples of buffering agents which could be utilized in such tablets include sodium bicarbonate, alkali earth metal salts such as calcium carbonate, calcium hydroxide, calcium lactate, calcium glycerophosphate, calcium acetate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide. A particular alkali earth metal salt useful for making an antacid tablet is calcium carbonate.

An example of a low density alkali earth metal salt useful for making the granules according to the present invention is extra light calcium carbonate available from Specialty Minerals Inc., Adams, Me. The density of the extra light calcium carbonate, prior to being processed according to the present invention, is about 0.37 gm/ml.

The granules used to make the tablets according to one embodiment of the present invention are made by either spray drying or pre-compacting the raw materials. Prior to being processed into granules by either process, the density

of the alkali earth metal salts useful in the present invention ranges from about 0.3 gm/ml to about 0.55 gm/ml, preferably about 0.35 gm/ml to about 0.45 gm/ml, even more preferably about 0.37 gm/ml to about 0.42 gm/ml.

Additionally, the present invention can be manufactured by utilizing micronized compounds in place of the granules or powder. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate. Although micronization results in increased surface area possibly causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole and other proton pump inhibitors.

The present invention also relates to administration kits to ease mixing and administration. A month's supply of powder or tablets, for example, can be packaged with a separate month's supply of diluent, and a re-usable plastic dosing cup. More specifically, the package could contain thirty (30) suspension tablets containing 20 mg omeprazole each, 1 L sodium bicarbonate 8.4% solution, and a 30 ml dose cup. The user places the tablet in the empty dose cup, fills it to the 30 ml mark with the sodium bicarbonate, waits for it to dissolve (gentle stirring or agitation may be used), and then ingests the suspension. One skilled in the art will appreciate that such kits may contain many different variations of the above components. For example, if the tablets or powder are compounded to contain PPI and buffering agent, the diluent may be water, sodium bicarbonate, or other compatible diluent, and the dose cup can be larger than 30 ml in size. Also, such kits can be packaged in unit dose form, or as weekly, monthly, or yearly kits, etc.

Although the tablets of this invention are primarily intended as a suspension dosage form, the granulations used to form the tablet may also be used to form rapidly disintegrating chewable tablets, lozenges, troches, or swallowable tablets. Therefore, the intermediate formulations as well as the process for preparing them provide additional novel aspects of the present invention.

Effervescent tablets and powders are also prepared in accordance with the present invention. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and tartaric acid. When the salts are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence."

The choice of ingredients for effervescent granules. depends both upon the requirements of the manufacturing process and the necessity of making a preparation which dissolves readily in water. The two required ingredients are at least one acid and at least one base. The base releases carbon dioxide upon reaction with the acid. Examples of such acids include, but are not limited to, tartaric acid and citric acid. Preferably, the acid is a combination of both tartaric acid and citric acid. Examples of bases include, but are not limited to, sodium carbonate, potassium bicarbonate and sodium bicarbonate. Preferably, the base is sodium bicarbonate, and the effervescent combination has a pH of about 6.0 or higher.

Effervescent salts preferably include the following ingredients, which actually produce the effervescence: sodium bicarbonate, citric acid and tartaric acid. When added to water the acids and base react to liberate carbon dioxide, resulting in effervescence. It should be noted that any acid-base combination which results in the liberation of carbon dioxide could be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use, and result in a pH of about 6.0 or higher.

It should be noted that it requires 3 molecules of $NaHCO3$ (sodium bicarbonate) to neutralize 1 molecule of citric acid and 2 molecules of $NaHCO3$ to neutralize 1 molecule of tartaric acid. It is desired that the approximate ratio of ingredients is as follows Citric Acid:Tartaric Acid:Sodium Bicarbonate=1:2:3.44 (by weight). This ratio can be varied and continue to produce an effective release of carbon dioxide. For example, ratios of about 1:0:3 or 0:1:2 are also effective.

The method of preparation of the effervescent granules of the present invention employs three basic processes: wet and dry granulation, and fusion. The fusion method is used for the preparation of most commercial effervescent powders. It should be noted that although these methods are intended for the preparation of granules, the formulations of effervescent salts of the present invention could also be prepared as tablets, according to well known prior art technology for tablet preparation.

Wet granulation is the oldest method of granule preparation. The individual steps in the wet granulation process of tablet preparation include milling and sieving of the ingredients; dry powder mixing; wet massing; granulation; and final grinding.

Dry granulation involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty rotary tablet press. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillation granulator. The individual steps include mixing of the powders; compressing (slugging); and grinding (slug reduction or granulation). No wet binder or moisture is involved in any of the steps.

The fusion method is the most preferred method for preparing the granules of the present invention. In this method, the compressing (slugging) step of the dry granulation process is eliminated. Instead, the powders are heated in an oven or other suitable source of heat.

PPIs Administered with Parietal Cell Activators

Applicant has unexpectedly discovered that certain compounds, such as chocolate, calcium and sodium bicarbonate and other alkaline substances, stimulate the parietal cells and enhance the pharmacologic activity of the PPI administered. For the purposes of this application, "parietal cell activator" shall mean any compound or mixture of compounds possessing such stimulatory effect including, but not limited to, chocolate, sodium bicarbonate, calcium (e.g., calcium carbonate, calcium gluconate, calcium hydroxide, calcium acetate and calcium glycerophosphate), peppermint oil, spearmint oil, coffee, tea and colas (even if decaffeinated), caffeine, theophylline, theobromine, and amino acids (particularly aromatic amino acids such as phenylalanine and tryptophan) and combinations thereof and the salts thereof.

Such parietal cell activators are administered in an amount sufficient to produce the desired stimulatory effect without causing untoward side effects to patients. For example, chocolate, as raw cocoa, is administered in an amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of other PPI). The dose of activator administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response (i.e., enhanced effect of PPI) over a reasonable time frame. The dose will be determined by the strength of the particular compositions employed and the condition of the person, as well as the body weight of the person to be treated. The size of the dose

also will be determined by the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular composition.

The approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other PPI) are:

Chocolate (raw cocoa)—5 mg to 2.5 g
Sodium bicarbonate—7 mEq to 25 mEq
Calcium carbonate—1 mg to 1.5 Gm
Calcium gluconate—1 mg to 1.5 Gm
Calcium lactate—1 mg to 1.5 Gm
Calcium hydroxide—1 mg to 1.5 Gm
Calcium acetate—0.5 mg to 1.5 Gm
Calcium glycerophosphate—0.5 mg to 1.5 Gm
Peppermint oil—(powdered form) 1 mg to 1 Gm
Spearmint oil—(powdered form) 1 mg to 1 Gm
Coffee—20 ml to 240 ml
Tea—20 ml to 240 ml
Cola—20 ml to 240 ml
Caffeine—0.5 mg to 1.5 GM
Theophylline—0.5 mg to 1.5 GM
Theobromine—0.5 mg to 1.5 GM
Phenylalanine—0.5 mg to 1.5 GM
Tryptophan—0.5 mg to 1.5 GM

Pharmaceutically acceptable carriers are well-known to those who are skilled in the art. The choice of carrier will be determined, in part, both by the particular composition and by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical compositions of the present invention.

EXAMPLE I

A. Fast Disintegrating Suspension Tablets of Omeprazole

A fast disintegrating tablet is compounded as follows: Croscarmellose sodium 300 g is added to the vortex of a rapidly stirred beaker containing 3.0 kg of deionized water. This slurry is mixed for 10 minutes. Omeprazole 90 g (powdered) is placed in the bowl of a Hobart mixer. After mixing, the slurry of croscarmellose sodium is added slowly to the omeprazole in the mixer bowl, forming a granulation which is then placed in trays and dried at 70° C. for three hours. The dry granulation is then placed in a blender, and to it is added 1,500 g of Avicel® AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 1,500 g of Avicel® PH-302 (microcrystalline cellulose). After this mixture is thoroughly blended, 35 g of magnesium stearate is added and mixed for 5 minutes. The resulting mixture is compressed into tablets on a standard tablet press (Hata HS). These tablets have an average weight of about 1.5 g, and contain about 20 mg omeprazole. These tablets have low friability and rapid disintegration time. This formulation may be dissolved in an aqueous solution containing a buffering agent for immediate oral administration.

Alternatively, the suspension tablet may be swallowed whole with a solution of buffering agent. In both cases, the preferred solution is sodium bicarbonate 8.4%. As a further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other PPI) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole with an aqueous diluent.

B. 10 mg Tablet Formula

Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg

C. 20 mg Tablet Formula

Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg

D. Tablet for Rapid Dissolution

Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Croscarmellose sodium	12 mg

E. Powder for Reconstitution for Oral Use (or per ng tube).

Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Glycerine	200 g

F. 10 mg Tablet Formula

Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	1 mg
Magnesium stearate	1 mg

G. 10 mg Tablet Formula

Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	200 mg
Calcium glycerophosphate	200 mg
Sodium bicarbonate	400 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg

EXAMPLE II

Standard Tablet of PPI and Buffering Agent

Ten (10) tablets were prepared using a standard tablet press, each tablet comprising about 20 mg omeprazole and about 975 mg sodium bicarbonate uniformly dispersed throughout the tablet. To test the dissolution rate of the tablets, each was added to 60 ml of water. Using previously prepared liquid omeprazole/sodium bicarbonate solution as a visual comparator, it was observed that each tablet was completely dispersed in under three (3) minutes.

Another study using the tablets compounded according to this Example evaluated the bioactivity of the tablets in five (5) adult critical care patients. Each subject was administered one tablet via ng with a small amount of water, and the pH of ng aspirate was monitored using paper measure. The pH for each patient was evaluated for 6 hours and remained above 4, thus demonstrating the therapeutic benefit of the tablets in these patients.

Tablets were also prepared by boring out the center of sodium bicarbonate USP 975 mg tablets with a knife. Most of the removed sodium bicarbonate powder was then triturated with the contents of a 20 mg Prilosec® capsule and the resulting mixture was then packed into the hole in the tablet and sealed with glycerin.

EXAMPLE III

PPI Central Core Tablet

Tablets are prepared in a two-step process. First, about 20 mg of omeprazole is formed into a tablet as is known in the art to be used as a central core. Second, about 975 mg sodium bicarbonate USP is used to uniformly surround the central core to form an outer protective cover of sodium bicarbonate. The central core and outer cover are both prepared using standard binders and other excipients to create a finished, pharmaceutically acceptable tablet.

EXAMPLE IV

Effervescent Tablets and Granules

The granules of one 20 mg Prilosec® capsule were emptied into a mortar and triturated with a pestle to a fine powder. The omeprazole powder was then geometrically diluted with about 958 mg sodium bicarbonate USP, about 832 mg citric acid USP and about 312 mg potassium carbonate USP to form a homogeneous mixture of effervescent omeprazole powder. This powder was then added to about 60 ml of water whereupon the powder reacted with the water to create effervescence. A bubbling solution resulted of omeprazole and principally the antacids sodium citrate and potassium citrate. The solution was then administered orally to one adult male subject and gastric pH was measured using pHydrion paper. The results were as follows:

Time Interval	pH Measured
Immediately prior to dose	2
1 hour post dose	7
2 hours post dose	6
4 hours post dose	6
6 hours post dose	5
8 hours post dose	4

One skilled in the art of pharmaceutical compounding will appreciate that bulk powders can be manufactured using the above ratios of ingredients, and that the a powder can be pressed into tablets using standard binders and excipients. Such tablets are then mixed with water to activate the effervescent agents and create the desired solution. In addition, lansoprazole 30 mg (or an equipotent dose of other PPI) can be substituted for omeprazole.

The effervescent powder and tablets can alternatively be formulated by employing the above mixture but adding an additional 200 mg of sodium bicarbonate USP to create a resulting solution with a higher pH. Further, instead of the excess 200 mg of sodium bicarbonate, 100 mg of calcium glycerophosphate or 100 mg of calcium lactate can be employed. Combinations of the same can also added.

EXAMPLE V

Parietal Cell Activator "Choco-Base™" Formulations and Efficacy

Children are affected by gastroesophageal reflux disease (GERD) with atypical manifestations. Many of these atypical symptoms are difficult to control with traditional drugs such as H_2-antagonists, cisapride, or sucralfate. PPIs are more effective in controlling gastric pH and the symptoms of GERD than other agents. However, PPIs are not available in dosage forms that are easy to administer to young children. To address this problem, applicant employed omeprazole or lansoprazole in a buffered chocolate suspension (Choco-Base, in children with manifestations of GERD.

Applicant performed a retrospective evaluation of children with GERD referred to the University of Missouri-Columbia from 1995 to 1998 who received treatment with the experimental omeprazole or lansoprazole Choco-Base suspension formulated in accordance with Formulation 1 stated below. Data were included on all patients with follow up information sufficient to draw conclusions about pre/post treatment (usually >6 months). There were 25 patients who met the criteria for this evaluation. Age range was several weeks to greater than 5 years. Most patients had a history of numerous unsuccessful attempts at ameliorating the effects of GERD. Medication histories indicated many trials of various drugs.

The primary investigator reviewed all charts for uniformity of data collection. When insufficient data was available in the University charts, attempts were made to review

charts in the local primary care physicians' offices for follow-up data. If information was still unavailable to review, attempts were made to contact family for follow-up. If data were still unavailable the patients were considered inevaluable.

Patient charts were reviewed in detail. Data noted were date of commencement of therapy, date of termination of therapy and any reason for termination other than response to treatment. Patient demographics were also recorded, as were any other medical illnesses. Medical illnesses were divided grossly into those that are associated with or exacerbate GERD and those that do not.

Patient charts were examined for evidence of response to therapy. As this was largely a referral population, and a retrospective review, quantification of symptomatology based on scores, office visits and ED visits was difficult. Therefore, applicant examined charts for evidence of an overall change in patient symptoms. In specific, any data to point towards improvement, decline or lack of change were examined and recorded.

Results.

A total of 33 pediatric patients to date have been treated with the above-described suspension at the University of Missouri—Columbia. Of the 33 patients, 9 were excluded from the study, all based upon insufficient data about commencement, duration or outcome in treatment with PPI therapy. This left 24 patients with enough data to draw conclusions.

Of the 24 remaining patients, 18 were males and 6 females. Ages at implementation of PPI therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months [mean of 37 mo.] Early on, reflux was usually documented by endoscopy and confirmed by pH probe. Eventually, pH probe was dropped and endoscopy was the sole method for documenting reflux, usually at the time of another surgery (most often T-tubes or adenoidectomy). Seven patients had pH probe confirmation of GERD, whereas 18 had endoscopic confirmation of reflux including all eight. who had pH probing done (See Graphs 1 and 2 below). Reflux was diagnosed on endoscopy most commonly by cobblestoning of the tracheal wall, with laryngeal and pharyngeal cobblestoning as findings in a few patients. Six patients had neither pH nor endoscopic documentation of GERD, but were tried on PPI therapy based on symptomatology alone.

Past medical history was identified in each chart. Ten patients had reflux-associated diagnoses. These were most commonly cerebral palsy, prematurity and Pierre Robin sequence. Other diagnoses were Charcot-Marie-Tooth disease, Velocardiofacial syndrome, Down syndrome and De George's syndrome. Non-reflux medical history was also identified and recorded separately (See Table 2 below). Patients were, in general, referral patients from local family practice clinics, pediatricians, or other pediatric health care professionals. Most patients were referred to ENT for upper airway problems, sinusitis, or recurrent/chronic otitis media that had been refractory to medical therapy as reported by the primary care physician. Symptoms and signs most commonly found in these patients were recorded and tallied. All signs and symptoms were broken down into six major categories: (1) nasal; (2) otologic; (3) respiratory; (4) gastrointestinal; (5) sleep-related; and (6) other. The most common problems fell into one or all of the first 3 categories (See Table 1 below).

Most patients had been treated in the past with medical therapy in the form of antibiotics, steroids, asthma medications and other diagnosis-appropriate therapies. In addition, nine of the patients had been on reflux therapy in the past, most commonly in the form of conservative therapy such as head of bed elevation 30°, avoidance of evening snacks, avoidance of caffeinated beverages as well as cisapride and ranitidine (See Graph 3 below).

The proton pump inhibitor suspension used in this group of patients was Choco-Base suspension of either lansoprazole or omeprazole. The dosing was very uniform, with patients receiving doses of either 10 or 20 mg of omeprazole and 23 mg of lansoprazole. Initially, in April of 1996 when therapy was first instituted 10 mg of omeprazole was used. There were 3 patients in this early phase who were treated initially with 10 mg po qd of omeprazole. All three subsequently were increased to either 20 mg po qd of omeprazole or 23 mg po qd of lansoprazole. All remaining patients were given either the 20 mg omeprazole or the 23 mg lansoprazole treatment qd, except in one case, where 30 mg of lansoprazole was used. Patients were instructed to take their doses once per day, preferably at night in most cases. Suspensions were all filled through the University of Missouri Pharmacy at Green Meadows. This allowed for tracking of usage through refill-data.

Most patients responded favorably to and tolerated the once daily dosing of Choco-Base proton pump inhibitor suspension. Two patients had documented adverse effects associated with the use of the PPI suspension. In one a patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment failure. The other patient had small amounts of bloody stools per mother. This patient never had his stool tested, as his bloody stool promptly resolved upon cessation of therapy, with no further sequellae. The other 23 patients had no documented adverse effects.

Patients were categorized based on review of clinic notes and chart review into general categories: (1) improved; (2) unchanged; (3) failed; and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of PPI therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical findings while on therapy, one complained of worsening symptoms while on therapy, one patient had therapy as prophylaxis for surgery, and two stopped therapy just after its commencement (see graph 4). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which PPI therapy was for purely prophylactic reasons, leaves (17/21) 81% of patients that responded to Choco-Base suspension. This means that 19% (4/21) of patients received no apparent benefit from PPI therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were mild bloody stool that completely resolved upon cessation of therapy.

Discussion.

GERD in the pediatric population is relatively common, affecting almost 50% of newborns. Even though most infants outgrow physiologic reflux, pathologic reflux still affects approximately 5% of all children, throughout childhood. Recently considerable data has pointed to reflux as an etiologic factor in extra-esophageal areas. GERD has been attributed to sinusitis, dental caries, otitis media, asthma, apnea, arousal, pneumonia, bronchitis, and cough, among others. Despite the common nature of reflux, there seems to have been little improvement in therapy for reflux, especially in the non-surgical arena.

The standard of therapy for the treatment of GERD in the pediatric population has become a progression from conservative therapy to a combination of a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, PPI therapy is effective in 90% of those treated for gastroesophageal reflux disease. As a medical alternative to

the H-2 blockers, the proton pump inhibitors have not been studied extensively in the pediatric population. Part of the reason for this lack of data may be related to the absence of a suitable dosage formulation for this very young population, primarily under 2 years of age, that does not swallow capsules or tablets. It would be desirable to have a true liquid formulation (solution or suspension) with good palatability such as is used for oral antibiotics, decongestants, antihistamines, H-2 blockers, cisapride, metoclopramide, etc. The use of lansoprazole granules (removed from the gelatin capule) and sprinkled on applesauce has been approved by the Food and Drug Administration as an alternative method of drug administration in adults but not in children. Published data are lacking on the efficacy of the lansoprazole sprinkle method in children. Omeprazole has been studied for bioequivalence as a sprinkle in adults and appears to produce comparable serum concentrations when compared to the standard capsule. Again no data are available on the omeprazole sprinkle in children. An additional disadvantage of omeprazole is its taste which is quinine-like. Even when suspended in juice, applesauce or the like, the bitter nature of the medicine is easily tasted even if one granule is chewed. For this reason applicant eventually progressed to use lansoprazole in Choco-Base. Pantoprazole and rabeprazole are available as enteric-coated tablets only. Currently, none of the proton pump inhibitors available in the United States are approved for pediatric use. There is some controversy as to what the appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective PPI dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity with the PPI's is not seen even at >50 mg/kg, there appears little risk associated with the higher dosages. Based on observations at the University of Missouri consistent with the findings of this review, applicant established a simple fixed dosage regimen of 10 ml Choco-Base suspension daily. This 10 ml dose provided 20 mg omeprazole and 23 mg lansoprazole.

In the ICU setting, the University of Missouri-Columbia has been using an unflavored PPI suspension given once daily per various tubes (nasogastric, g-tube, jejunal feeding tube, duo tube, etc.) for stress ulcer prophylaxis. It seemed only logical that if this therapy could be made into a palatable form, it would have many ideal drug characteristics for the pediatric population. First, it would be liquid, and therefore could be administered at earlier ages. Second, if made flavorful it could help to reduce noncompliance. Third, it could afford once daily dosing, also helping in reducing noncompliance. In the process, applicant discovered that the dosing could be standardized, which nearly eliminated dosing complexity.

Choco-Base is a product which protects drugs which are acid labile, such as proton pump inhibitors, from acid degradation. The first few pediatric patients with reflux prescribed Choco-Base were sicker patients. They had been on prior therapy and had been diagnosed both by pH probe and endoscopy. In the first few months, applicant treated patients with 10 mg of omeprazole qd (1 mg/kg) and found this to be somewhat ineffective, and quickly increased the dosing to 20 mg (2 mg/kg) of omeprazole. About halfway through the study, applicant began using lansoprazole 23 mg po qd. Applicant's standard therapy was then either 20 mg of omeprazole or 23 mg of lansoprazole once daily. The extra 3 mg of lansoprazole is related only to the fact that the final concentration was 2.25 mg/ml, and applicant desired to keep dosing simple, so he used a 10 ml suspension.

The patients that were treated represented a tertiary care center population, and they were inherently sicker and refractory to medical therapy in the past. The overall 72% success rate is slightly lower than the 90% success rates of PPIs in the adult population, but this can be attributed to the refractory nature of their illness, most having failed prior non-PPI treatment. The population in this study is not indicative of general practice populations.

Conclusion.

PPI therapy is a beneficial therapeutic option in the treatment of reflux related symptoms in the pediatric population. Its once daily dosing and standard dosing scheme combined with a palatable formulation makes it an ideal pharmacologic agent.

TABLE 1

Symptoms	Patient Numbers
Nasal:	35
Sinusitis	7
Congestion	8
Nasal discharge	16
Other	4
Otologic:	26
Otitis Media	17
Otorrhea	9
Respiratory:	34
Cough	10
Wheeze	11
Respiratory Distress:	5
Pneumonia	2
Other	6
Gastrointestinal:	10
Abdominal Pain	1
Reflux/Vomiting	4
Other	4
Sleep Disturbances:	11
Other	2

TABLE 2

Past Medical History	Number of Patients
Reflux Associated:	12
Premature	5
Pierre-Robin	2
Cerebral Palsy	2
Down Syndrome	1
Charcot-Marie-Tooth	1
Velocardiofacial Syndrome	1
Other Medical History	12
Cleft Palate	3
Asthma	3
Autism	2
Seizure Disorder	1
Diabetes Mellitus	1
Subglottic Stenosis	1
Tracheostomy Dependent	1

FORMULATION 1

PART A INGREDIENTS	AMOUNT (mg)
Omeprazole	200
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150

-continued

Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT (ml)**
Distilled Water	100
COMPOUNDING INSTRUCTIONS	
Add Part B to Part A to create a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.	

FORMULATION 2

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT**
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg
COMPOUNDING INSTRUCTIONS	
Mix the constituents of Part B together thoroughly and then add to Part A. This results in a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.	

FORMULATION 3

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT**
Distilled Water	100 ml
Omeprazole	200 mg
COMPOUNDING INSTRUCTIONS	
This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.	

-continued

FORMULATION 4

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT**
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg
COMPOUNDING INSTRUCTIONS	
This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.	

In all four of the above formulations, lansoprazole or other PPI can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200 mg of omeprazole. Additionally, aspartame can be substituted for sucrose, and the following other ingredients can be employed as carriers, adjuvants and excipients: maltodextrin, vanilla, carrageenan, mono and diglycerides, and lactated monoglycerides. One skilled in the art will appreciate that not all of the ingredients are necessary to create a Choco-Base formulation that is safe and effective.

Omeprazole powder or enteric coated granules can be used in each formulation. If the enteric coated granules are used, the coating is either dissolved by the aqueous diluent or inactivated by trituration in the compounding process.

Applicant additionally analyzed the effects of a lansoprazole Choco-Base formulation on gastric pH using a pH meter (Fisher Scientific) in one adult patient versus lansoprazole alone. The patient was first given a 30 mg oral capsule of Prevacid®, and the patient's gastric pH was measured at 0, 4, 8, 12, and 16 hours post dose. The results are illustrated in FIG. 4.

The Choco-Base product was compounded according to Formulation 1 above, except 300 mg of lansoprazole was used instead of omeprazole. A dose of 30 mg lansoprazole Choco-Base was orally administered at hour 18 post lansoprazole alone. Gastric pH was measured using a pH meter at hours 18, 19, 24, 28, 32, 36, 40, 48, 52, and 56 post lansoprazole alone dose.

FIG. 4 illustrates the lansoprazole/cocoa combination resulted in higher pH_s at hours 19–56 than lansoprazole alone. at hours 4–18. Therefore, the combination of the lansoprazole with chocolate enhanced the pharmacologic activity of the lansoprazole. The results establish that the sodium bicarbonate as well as chocolate flavoring and calcium were all able to stimulate the activation of the proton pumps, perhaps due to the release of gastrin. Proton pump inhibitors work by functionally inhibiting the proton pump and effectively block activated proton pumps

(primarily those inserted into the secretory canalicular membrane) By further administering the proton pump inhibitor with one of these activators or enhancers, there is a synchronization of activation of the proton pump with the absorption and subsequent parietal cell concentrations of the proton pump inhibitor. As illustrated in FIG. 4, this combination produced a much longer pharmacologic effect than when the proton pump inhibitor was administered alone.

EXAMPLE VI

Combination Tablet Delivering Bolus and Time-released Doses of PPI

Tablets were compounded using known methods by forming an inner core of 10 mg omeprazole powder mixed with 750 mg sodium bicarbonate, and an outer core of 10 mg omeprazole enteric-coated granules mixed with known binders and excipients. Upon ingestion of the whole tablet, the tablet dissolves and the inner core is dispersed in the stomach where it is absorbed for immediate therapeutic effect. The enteric-coated granules are later absorbed in the duodenum to provide symptomatic relief later in the dosing cycle. This tablet is particularly useful in patients who experience breakthrough gastritis between conventional doses, such as while sleeping or in the early morning hours.

EXAMPLE VII

Therapeutic Application

Patients were evaluable if they met the following criteria: had two or more risk factors for SRMD (mechanical ventilation, head injury, severe burn, sepsis, multiple, trauma, adult respiratory distress syndrome, major surgery, acute renal failure, multiple operative procedures, coagulotherapy, significant hyportension, acid-base disorder, and hepatic failure), gastric pH of ≦4 prior to study entry, and no concomitant prophylaxis for SRMD.

The omeprazole solution was prepared by mixing 10 ml of 8.4% sodium bicarbonate with the contents of a 20 mg capsule of omeprazole (Merck & Co.. Inc., West Point, Pa.) to yield. a solution having a final omeprazole concentration of 2 mg/ml.

Nasogastric (ng) tubes were placed in the patients and an omeprazole dosage protocol of buffered 40 mg omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$—8.4%) followed by 40 mg of the same buffered omeprazole solution in eight hours, then 20 mg of the same buffered omeprazole solution per day, for five days. After each buffered omeprazole solution administration, nasogastric suction was turned off for thirty minutes.

Eleven patients were evaluable. All patients were mechanically ventilated. Two hours after the initial 40 mg dose of buffered omeprazole solution, all patients had an increase in gastric pH to greater than eight as shown in FIG. 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four when administered 20 mg omeprazole solution. One patient required 40 mg omeprazole solution per day (closed head. injury, five total risk factors for SRMD). Two patients were changed to omeprazole solution after having developed clinically significant upper gastrointestinal bleeding while receiving conventional intravenous H_2-antagonists. Bleeding subsided in both cases after twenty-four hours. Clinically significant upper gastrointestinal bleeding did not occur in the other nine patients. Overall mortality was 27%, mortality attributable to upper gastrointestinal bleeding was 0%. Pneumonia developed in one patient after initiating omeprazole therapy and was present upon the initiation of omeprazole therapy in another patient. The mean length of prophylaxis was five days.

A pharmacoeconomic analysis revealed a difference in the total cost of care for the prophylaxis of SRMD:

ranitidine (Zantac®) continuous infusion intravenously (150 mg/24 hours)×five days $125.50;

cimetidine (Tagamet®) continuous infusion intravenously (900 mg/24 hours)×five days $109.61;

sucralfate one gm slurry four times a day per (ng) tube×five days $73.00; and

buffered omeprazole solution regimen per (ng) tube×five days $65.70.

This example illustrates the efficacy of the buffered omeprazole solution of the present invention based on the increase in gastric pH, safety and cost of the buffered omeprazole solution as a method for SRMD prophylaxis.

EXAMPLE VIII

Effect on pH

Experiments were carried out in order to determine the effect of the omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$—8.4%) administration on the accuracy of subsequent pH measurements through a nasogastric tube.

After preparing a total of 40 mg of buffered omeprazole solution, in the manner of Example VII, doses were administered into the stomach, usually, through a nasogastric (ng) tube. Nasogastric tubes from nine different institutions were gathered for an evaluation. Artificial gastric fluid (gf) was prepared according to the USP. pH recordings were made in triplicate using a Microcomputer Portable pH meter model 6007 (Jenco Electronics Ltd., Taipei, Taiwan).

First, the terminal portion (tp) of the nasogastric tubes was placed into a glass beaker containing the gastric fluid. A 5 ml aliquot of gastric fluid was aspirated through each tube and the pH recorded; this was called the "pre-omeprazole solution/suspension measurement." Second, the terminal portion (tp) of each of the nasogastric tubes was removed from the beaker of gastric fluid and placed into an empty beaker. Twenty (20) mg of omeprazole solution was delivered through each of the nasogastric tubes and flushed with 10 ml of tap water. The terminal portion (tp) of each of the nasogastric tubes was placed back into the gastric fluid. After a one hour incubation, a 5 ml aliquot of gastric fluid was aspirated through each nasogastric tube and the pH recorded; this was called the "after first dose SOS [Simplified Omeprazole Solution] measurement." Third, after an additional hour had passed, the second step was repeated; this was called the "after second dose SOS [Simplified Omeprazole Solution] measurement." In addition to the pre-omeprazole measurement, the pH of the gastric fluid was checked in triplicate after the second and third steps. A change in the pH measurements of +/− 0.3 units was considered significant. The Friedman test was used to compare the results. The Friedman test is a two way analysis of variance which is used when more than two related samples are of interest, as in repeated measurements.

The results of these experiments are outlined in Table 1.

TABLE 1

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
[1] gf Pre SOS	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[2] gf p 1st dose 1.3←check of fg pH	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[3] gf p 2nd Dose 1.3←check of gf pH	1.3	1 3	1.4	1.4	1.4	1.3	1.4	1.3	1.3

SOS pH = 9.0

Table 1 illustrates the results of the pH measurements that were taken during the course of the experiment. These results illustrate that there were no statistically significant latent effects of omeprazole solution administration (per nasogastric tube) on the accuracy of subsequent pH measurements obtained through the same nasogastric tube.

EXAMPLE IX

Efficacy of Buffered Omeprazole Solution in Ventilated Patients

Experiments were performed in order to determine the efficacy, safety, and cost of buffered omeprazole solution in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Patients: Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage.

Interventions: Patients received 20 ml omeprazole solution (prepared as per Example VII and containing 40 mg of omeprazole) initially, followed by a second 20 ml dose six to eight hours later, then 10 ml (20 mg) daily. Omeprazole solution according to the present invention was administered through a nasogastric tube, followed by 5–10 ml of tap water. The nasogastric tube was clamped for one to two hours after each administration.

Measurements and Main Results: The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage and was associated with a five percent decrease in hematocrit. Secondary efficacy measures were gastric pH measured four hours after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the incidence of adverse events and the incidence of pneumonia. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric pH was 7.1 (mean), the mean gastric pH after starting omeprazole was 6.8 (mean) and the lowest pH after starting omeprazole was 5.6 (mean). The incidence of pneumonia was twelve percent. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions: Omeprazole solution prevented clinically significant upper, gastrointestinal bleeding and maintained gastric pH above 5.5 in mechanically ventilated critical care patients without producing toxicity.

Materials and Methods

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population: All adult (>18 years old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated intensive care unit stay of at least forty-eight hours were considered for inclusion in the study. To be included patients also had to have a gastric pH of <4, had to be mechanically ventilated and have one of the following additional risk factors for a minimum of twenty-four hours after initiation of omeprazole suspension: head injury with altered level of consciousness, extensive burns (>20% Body Surface Area), acute renal failure, acid-base disorder, multiple trauma, coagulopathy, multiple operative procedures, coma, hypotension for longer than one hour or sepsis (see Table 2). Sepsis was defined as the presence of invasive. pathogenic organisms or their toxins in blood or tissues resulting in a systematic response that included two or more of the following: temperature greater than 38° C. or less than 36° C., heart rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute (or $_pO_2$ less than 75 mm Hg), and white blood cell count greater than 12,000 or less than 4,000 cells/mm^3 or more than 10 percent bands (Bone, Let's Agree on Terminology: Definitions of Sepsis, Crit. Care Med., 19: 27 (1991)). Patients in whom H_2-antagonist therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count less than 30,000 cells/mm^3) ; were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH above four for forty-eight hours after ICU admission (without, prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having non-stress-related mucosal bleeding. The reason for this exclusion is the confounding effect of non-stress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration: Omeprazole solution was prepared immediately before administration by the patient's nurse using the following instructions: empty the contents of one or two 20 mg omeprazole capsule(s) into an empty 10 ml syringe (with 20 gauge needle in place) from which the plunger has been removed. (Omeprazole delayed-release capsules, Merck & Co., Inc., West Point, Pa.); replace the plunger and uncap the needle; withdraw 10 ml of 8.4% sodium bicarbonate solution or 20 ml if 40 mg given (Abbott Laboratories, North Chicago, Ill.), to create a concentration of 2 mg omeprazole per ml of 8.4% sodium bicarbonate; and

allow the enteric coated pellets of omeprazole to completely breakdown, 30 minutes (agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before administration. The solution was not administered with acidic substances. A high pressure liquid chromatography study was performed that demonstrated that this preparation of simplified omeprazole suspension maintains >90% potency for seven days at room temperature. This preparation remained free of bacterial and fungal contamination for thirty days when stored at room temperature (See Table 5).

The initial dose of omeprazole solution was 40 mg, followed by a second 40 mg dose six to eight hours later, then a 20 mg daily dose administered at 8:00 AM. Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5–10 ml of tap water and clamped for at least one hour. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube was removed and the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures: The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-minute lavage or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, Calif.) positive coffee ground material for four consecutive hours that did not clear with lavage (at least 100 ml) and produced a 5% decrease in hematocrit.

Secondary Outcome Measures: The secondary efficacy measures were gastric pH measured four hours after omeprazole was administered, mean gastric pH after starting omeprazole and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, N.Y.) was used to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of one pH unit. Gastric pH was measured before the initiation of omeprazole solution therapy, immediately before each dose, and every four hours between doses.

Other secondary outcome measures were incidence of adverse events (including drug interactions) and pneumonia. Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Prevention and Control definition of nosocomial pneumonia (Garner et al., 1988). According to these criteria, a patient who has pneumonia is one who has rales or dullness to percussion on physical examination of the chest or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and has at least two of the following present: new purulent sputum or changes in character of the sputum, an organism isolated from blood culture, fever or leukocytosis, or evidence of infection from a protective specimen brush or bronchoalveolar lavage. Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia incidence figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present prior to the start of omeprazole suspension.

Cost of Care Analysis: A pharmacoeconomic evaluation of stress ulcer prophylaxis using omeprazole solution was performed. The evaluation included total drug cost (acquisition and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental confusion), costs associated with clinically significant upper gastrointestinal bleeding. Total drug cost was calculated by adding the average institutional costs of omeprazole 20 mg capsules, 50 ml sodium bicarbonate vials, and 10 ml syringes with needle; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

Statistical Analysis: The paired t-test (two-tailed) was used to compare gastric pH before and after omeprazole solution administration and to compare gastric pH before omeprazole solution administration with the mean and lowest gastric pH value measured after beginning omeprazole.

Results:

Seventy-seven patients met the inclusion and exclusion criteria and received omeprazole solution (See FIG. 2). Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down prior to the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above six as soon as the patient was given a dose of omeprazole solution (in which the enteric coated pellets of omeprazole had been allowed to completely breakdown).

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained above four in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared failures, their pH values were no longer followed.

The ages of the remaining seventy-five patients ranged from eighteen to eighty-seven years; forty-two patients were male and thirty-three were female. All patients were mechanically ventilated during the study. Table 2 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was two to ten, with a mean of 3 (±1) (standard deviation). Five patients enrolled in the study had developed clinically significant bleeding while receiving continuous infusions of ranitidine (150 mg/24 hr) or cimetidine (900 mg/24 hr). In all five cases, the bleeding subsided and the gastric pH rose to above five within thirty-six hours after initiating omeprazole therapy. Three patients were enrolled after having developed two consecutive gastric pH values below three while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH rose to above five within four hours after omeprazole therapy was initiated. Four other patients were enrolled in this study after experiencing confusion (n=2) or thrombocytopenia (n=2) during H_2-antigens therapy. Within thirty-six hours of switching therapy, these adverse events resolved.

Stress-related Mucosal Bleeding and Mortality: None of the sixty-five patients who received buffered omeprazole solution as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant

upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only (Gastroccult-positive) within eighteen hours of starting omeprazole solution; bleeding stopped in all patients within thirty-six hours. The overall mortality rate in this group of critically ill patients was eleven percent. No death was attributable to upper gastrointestinal bleeding or the use of omeprazole solution.

Gastric pH: The mean (±standard deviation) pre-omeprazole gastric pH was 3.5±1.9. Within four hours of omeprazole administration, the gastric pH rose to 7.1±1.1 (See FIG. 3); this difference was significant (p<0.001). The differences between pre-omeprazole gastric pH and the mean and lowest gastric pH measurements during omeprazole administration (6.8±0.6 and 5.6±1.3, respectively) were also statistically significant (p<0.001).

Safety: Omeprazole solution was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have been drug-related thrombocytopenia. However, the platelet count continued to fall after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus was unable to continue on omeprazole. No. clinically. significant drug interactions with omeprazole were noted during the study period. As stated above, metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in omeprazole solution was small (12 mEq/10 ml) and no electrolyte abnormalities were found.

Pneumonia: Pneumonia developed in nine (12%) patients receiving omeprazole solution. Pneumonia was present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic evaluation: The average length of treatment was nine days. The cost of care data are listed in Tables 3 and 4. The costs of drug acquisition, preparation, and delivery for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 3. There were no costs to add from toxicity associated with omeprazole solution. Since two of seventy-five patients required 40 mg of omeprazole solution daily to adequately control gastric pH, the acquisition/preparation cost should reflect this. The additional 20 mg of omeprazole with vehicle adds seven cents per day to the cost of care. Therefore, the daily cost of care for omeprazole solution in the prophylaxis of stress-related mucosal bleeding was $12.60 (See Table 4).

Omeprazole solution is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has been challenged recently. All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage—mechanical ventilation. Previous trials and data from a recently published study show that stress ulcer prophylaxis is of proven benefit in patients at risk and, therefore, it was thought to be unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during omeprazole solution therapy. Gastric pH was maintained above 4 on omeprazole 20 mg/day in seventy-three of seventy-five patients. No adverse events or drug interaction associated with omeprazole were encountered.

TABLE 2

Mech Vent	Major Surgery	Multi-trauma	Head Injury	Hypo-tension	Renal Failure	Sepsis	Multiple Operation	Acid/ Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2

Risk factors present in patients in this study (n = 75)

TABLE 3

		Per day
RANITIDINE (day-9)		
Rantidine	150 mg/24 hr	6.15
Ancillary Product (1)	Piggyback (60%)	0.75
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs x 50%)	14.50
TOTAL far 9 days	→	304.20
RANITIDINE Cost per day	→	33.80
CIMETIDINE (day 1-9)		
Cimetidine	900 mg/24 hr	3.96
Ancillary Product (1)	Piggyback	1.25
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs x 50%)	14.50
TOTAL for 9 days	→	288.99
CIMETIDINE Cost per day	→	32.11
SUCRALFATE (day 1-9)		
Sucralfate	1 Gm x 4	2.40
Ancillary Product (1)	syringe	.20
Sterile Prep required	no	
R.N. time ($24/hr)	30 minutes/day (includes pH monitoring)	12.00
TOTAL for 9 days	→	131.40
SUCRALFATE Cost per day	→	14.60

Note: Does not include the cost of failure and/or adverse effect.
Acquisition, preparation and delivery costs of traditional agents.

EXAMPLE X

Bacteriostatic and Fungistatic Effects of Omeprazole Solution

The antimicrobial or bacteriostatic effects of the omeprazole solution were analyzed by applicant. An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made according to the present invention was stored at room temperature for four weeks and then was analyzed for fungal and bacterial growth. Following four weeks of storage at room temperature, no bacterial or fungal growth was detected.

An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made in accordance with the present invention was stored at room temperature for twelve weeks and then was analyzed for fungal and bacterial growth. After twelve weeks of incubation at room temperature, no fungal or bacterial growth was detected.

The results of these experiments illustrate the bacteriostatic and fungistatic characteristics of the omeprazole solution of the present invention.

EXAMPLE XI

Bioequivalency Study

Healthy male and female study participants over the age of 18 will be randomized to receive omeprazole in the following forms:

(a) 20 mg of a liquid formulation of approximately 20 mg. omeprazole in 4.8.mEq sodium bicarbonate qs to 10 ml with water;

(b) 20 mg of a liquid formulation of approximately 2 mg omeprazole per 1 ml of 8.4% sodium bicarbonate.

(c) Prilosec® (omeprazole) 20 mg capsule;

(d) Capsule prepared by inserting the contents of an omeprazole 20 mg capsule into a #4 empty gelatin capsule (Lilly) uniformly dispersed in 240 mg of sodium bicarbonate powder USP to form an inner capsule. The inner capsule is then inserted into a #00 empty gelatin capsule (Lilly) together with a homogeneous mixture of 600 mg sodium bicarbonate USP and110 mg pregelatinized starch NF.

Methodology

After appropriate screening and consent, healthy volunteers will be randomized to receive one of the following four regimens as randomly assigned by Latin Square. Each subject will be crossed to each regimen according to the randomization sequence until all subjects have received all four regimens (with one week separating each regimen).

Regimen A (20 mg omeprazole in 4.8 mEq sodium bicarbonate in 10 ml volume); Regimen B (20 mg omeprazole in 10 ml 8.4% sodium bicarbonate in 10 ml volume); Regimen C (an intact 20 mg omeprazole capsule); Regimen D (Capsule in capsule formulation, see above). For each dose/week, subjects will have an i.v. saline lock placed for blood sampling. For each regimen, blood samples will be taken over 24 hours a total of 16 times (with the last two specimens obtained 12 hours and 24 hours after drug administration).

Patient Eligibility

Four healthy females and four healthy males will be consented for the study.

Inclusion Criteria

Signed informed consent.

Exclusion Criteria

1. Currently taking H_2-receptor antagonist, antacid, or sucralfate.
2. Recent (within 7 days) therapy with lansoprazole, omeprazole, or other proton pump inhibitor.
3. Recent (within 7 days) therapy with warfarin.
4. History of variceal bleeding.
5. History of peptic ulcer disease or currently active G.I. bleed.
6. History of vagotomy or pyloroplasty.
7. Patient has received an investigational drug within 30 days.
8. Treatment with ketoconazole or itraconazole.
9. Patient has an allergy to omeprazole.

Pharmocokinetic Evaluation and Statistical Analysis

Blood samples will be centrifuged within 2 hours of collection and the plasma will then separated and frozen at −10° C. (or lower) until assayed. Pharmacokinetic variables will include: time to peak concentration, mean peak concentration, AUC (0-t) and (0-infinity). Analysis of variance will be used to detect statistical difference. Bioavailability will be assessed by the 90% confidence interval of the two one-sided tests on the natural logarithm of AUC.

HPLC Analysis

Omeprazole and internal standard (H168/24) will be used. Omeprazole and internal standard will be measured by modification of the procedure described by Amantea and Narang. (Amantea Mass., Narang PK. Improved Procedure for Quantification of Omeprazole and Metabolites Using Reversed-Phased High Performance Liquid Chromotography. J. Chromatography 426; 216–222. 1988). Briefly, 20 ul of omeprazole 2 mg/ml $NaHCO_3$ or Choco-Base omeprazole suspension and 190 ul of the internal standard are vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml of dichloroethane, 5 ml of hexane, and 980 ul of sterile water. After the sample is centrifuged, the organic layer is extracted and dried over a nitrogen stream. Each pellet is reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul is injected onto a C_{18} 5 U column equilibrated with the same mobile phase at 1.1 ml/min. Under these conditions, omeprazole is eluted at approximately 5 minutes, and the internal standard at approximately 7.5 minutes. The standard curve is linear over the concentration range 0–3 mg/ml (in previous work with SOS), and the between-day coefficient of variation has been <8% at all concentrations. The typical mean R2 for the standard curve has been 0.98 in prior work with SOS (omeprazole 2 mg/ml $NaHCO_3$ 8.4%).

Applicant expects that the above experiments will demonstrate there is more rapid absorption of formulations (a), (b) and (d) as compared to the enteric coated granules of formulation (c). Additionally, applicant expects that although there will be a difference in the rates of absorption among forms (a) through (d), the extent of absorption (as measured by the area under the curve (AUC)) should be similar among the formulations (a) through (d).

EXAMPLE XII

Intraveneous PPI in Combination With Oral Parietal Cell Activator

Sixteen (16) normal, healthy male and female study subjects over the age of 18 will be randomized to receive pantoprazole as follows:

(a) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of sodium bicarbonate 8.4%; and

(b) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of water.

The subjects will receive a single dose of (a) or (b) above, and will be crossed-over to (a) and (b) in random fashion. Serum concentrations of pantoprazole versus time after administration data will be collected, as well as. gastric pH control as measured with an indwelling pH probe.

Further, similar studies are contemplated wherein chocolate or other parietal cell activator is substituted for the parietal cell activator sodium bicarbonate, and other PPIs are substituted for pantoprazole. The parietal cell activator can be administered either within about 5 minutes before, during or within about 5 minutes after the IV dose of PPI.

Applicant expects that these studies will demonstrate that significantly less IV PPI is required to achieve therapeutic effect when it is given in combination with an oral parietal cell activator.

Additionally, administration kits of IV PPI and oral parietal cell activator can be packaged in many various forms for ease of administration and to optimize packing and shipping the product. Such kits can be in unit dose or multiple dose form.

EXAMPLE XIII

Twelve (12) Month Stability of Omeprazole Solution

A solution was prepared by mixing 8.4% sodium bicarbonate with omeprazole to produce a final concentration of 2 mg/ml to determine the stability of omeprazole solution after 12 months. The resultant preparation was stored in clear glass at room temperature, refrigerated and frozen. Samples were drawn after thorough agitation from the stored preparations at the prescribed times. The samples were then stored at 70° C. Frozen samples remained frozen until they were analyzed. When the collection process was completed, the samples were shipped to a laboratory overnight on dry ice for analysis. Samples were agitated for 30 seconds and sample aliquots were analyzed by HPLC in triplicate according to well known methods. Omeprazole and the internal standard were measured by a modification of the procedure described by Amantea and Narang. Amantea Mass., Narang PK, Improved Procedure For Quantitation Of Omeprazole And Metabolites Using Reverse-Phased High-Performance Liquid Chromatography, J. Chromatography, 426: 216–222 (1988). Twenty (20) ul of the omeprazole 2 mg/ml $NaHCO_3$ solution and 100 ul of the internal standard solution were vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml dichloroethane, 5 ml hexane, and 980 ul of sterile water. The sample was centrifuged and the organic layer was extracted and dried over a nitrogen stream. Each pellet was reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul were injected onto a C185u column equilibrated with the same mobile phase at 1.1 ml/min. Omeprazole was eluted at ~5 min, and the internal standard at ~7.5 min. The standard curve was linear over the concentrated range 0–3 mg/ml, and between-day coefficient of variation was <8% at all concentrations. Mean R2 for the standard curve was 0.980.

The 12 month sample showed stability at greater than 90% of the original concentration of 2 mg/ml. (i.e., 1.88 mg/ml, 1.94 mg/ml, 1.92 mg/ml).

Throughout this application various publications and patents are referenced by citation and number. The disclosure of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation. Obviously, many modifications, equivalents, and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described.

I claim:

1. A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and

(b) at least one buffering agent selected from the group consisting of sodium bicarbonate, potassium bicarbonate, a calcium salt, and a magnesium salt, in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor; wherein the dosage form is selected from the group consisting of suspension tablet, chewable tablet, effervescent powder, and effervescent tablet.

2. The composition as recited in claim 1, wherein the proton pump inhibitor is omeprazole.

3. The composition as recited in claim 1, wherein the proton pump inhibitor is lansoprazole.

4. The composition as recited in claim 1, wherein the proton pump inhibitor is rabeprazole.

5. The composition as recited in claim 1, wherein the proton pump inhibitor is esomeprazole.

6. The composition as recited in claim 1, wherein the proton pump inhibitor is pantoprazole.

7. The composition as recited in claim 1, wherein the proton pump inhibitor is pariprazole.

8. The composition as recited in claim 1, wherein the proton pump inhibitor is leminoprazole.

9. The composition as recited in claim 1, further comprising at least one flavoring agent.

10. The composition as recited in claim 1, further comprising an anti-foaming agent.

11. The composition as recited in claim 1, wherein the dosage form is a suspension tablet.

12. The composition as recited in claim 1, wherein the dosage form is a chewable tablet.

13. The composition as recited in claim 12, further comprising aspartame.

14. The composition as recited in claim 1, wherein the dosage form is an effervescent powder.

15. The composition as recited in claim 1, wherein the dosage form is an effervescent tablet.

16. The composition as recited in claim 1, wherein the buffering agent is at least about 1680 mg sodium bicarbonate.

17. The composition as recited in claim 1, wherein the buffering agent is about 1000 mg to about 1680 mg sodium bicarbonate.

18. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 11 with an aqueous medium.

19. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 12 with an aqueous medium.

20. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 14 with an aqueous medium.

21. A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in claim 15 with an aqueous medium.

22. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form of claim 1 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

23. The method as recited in claim 22, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

24. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject a solid pharmaceutical composition in a dosage form that is not enteric-coated; wherein the composition comprises active ingredients consisting essentially of:

(a) a therapeutically effective amount of approximately 5 mg to approximately 300 mg of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole,

esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent in an amount of approximately 1.0 mEq to approximately 150 mEq selected from the group consisting of a bicarbonate salt of a group IA metal, a calcium salt, and a magnesium salt, wherein the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.

25. The method of claim 24, wherein the calcium salt is selected from the group consisting of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium bicarbonate, calcium gluconate, and other calcium salts.

26. The method of claim 24, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg.

27. The method of claim 24, wherein the sodium bicarbonate is in an amount of at least about 1680 mg.

28. The method of claim 24, wherein the calcium salt is calcium carbonate present in an amount from about 250 mg to about 1000 mg.

29. The method of claim 24, wherein the calcium salt is calcium carbonate present in an amount from about 500 mg to about 1000 mg.

30. The method of claim 24, wherein the calcium salt is calcium carbonate present in an amount of at least about 1000 mg.

31. The method of claim 24, wherein the buffering agent is in an amount of at least 10 mEq.

32. The method of claim 24, wherein the buffering agent is in an amount from about 10 mEq to about 70 mEq.

33. The method of claim 24, wherein the buffering agent is in an amount from about 20 mEq to about 40 mEq.

34. The method of claim 24, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

35. The method of claim 24, wherein the proton pump inhibitor is omeprazole.

36. The method of claim 35, wherein the omeprazole is present in an amount of about 10 mg.

37. The method of claim 35, wherein the omeprazole is present in an amount of about 20 mg.

38. The method of claim 35, wherein the omeprazole is present in an amount of about 40 mg.

39. The method of claim 35, wherein the omeprazole is present in an amount of about 60 mg.

40. The method of claim 35, wherein the omeprazole is present in an amount of about 80 mg.

41. The method of claim 35, wherein the omeprazole is present in an amount of about 100 mg.

42. The method of claim 24, wherein the proton pump inhibitor is lansoprazole.

43. The method of claim 42, wherein the lansoprazole is present in an amount of about 15 mg.

44. The method of claim 42, wherein the lansoprazole is present in an amount of about 30 mg.

45. The method of claim 42, wherein the lansoprazole is present in an amount of about 45 mg.

46. The method of claim 42, wherein the lansoprazole is present in an amount of about 60 mg.

47. The method of claim 42, wherein the lansoprazole is present in an amount of about 90 mg.

48. The method of claim 42, wherein the lansoprazole is present in an amount of about 100 mg.

49. The method of claim 24, wherein the proton pump inhibitor is micronized.

50. The method of claim 24, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

51. The method of claim 24, wherein the subject is a human.

52. The method of claim 24, wherein the dosage form further comprises a flavoring agent.

53. The method of claim 52, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

54. The method of claim 24, wherein the composition is provided as a separate component of a kit.

55. The method of claim 24, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

56. The method of claim 24, wherein the dosage form is administered once or twice a day.

57. A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent selected from the group consisting of sodium bicarbonate, and calcium carbonate, in an amount more than about 40 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

58. The composition as recited in claim 57, wherein the buffering agent is sodium bicarbonate.

59. The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount from about 400 mg to about 4000 mg.

60. The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

61. The composition as recited in claim 57, wherein the buffering agent is calcium carbonate.

62. The composition as recited in claim 57, wherein the calcium carbonate is in an amount from about 400 mg to about 4000 mg.

63. The composition as recited in claim 61, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

64. The composition as recited in claim 61, wherein the calcium carbonate is in an amount of at least about 800 mg.

65. The composition as recited in claim 57, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

66. The composition as recited in claim 57, wherein the proton pump inhibitor is omeprazole.

67. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 10 mg.

68. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 20 mg.

69. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 40 mg.

70. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 60 mg.

71. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 80 mg.

72. The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 100 mg.

73. The composition as recited in claim 57, wherein the proton pump inhibitor is lansoprazole.

74. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 15 mg.

75. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 30 mg.

76. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 45 mg.

77. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 60 mg.

78. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 90 mg.

79. The composition as recited in claim 73, wherein the lansoprazole is present in an amount of about 100 mg.

80. The composition as recited in claim 57, wherein the proton pump inhibitor is micronized.

81. The composition as recited in claim 57, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

82. The composition as recited in claim 57, further comprising a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

83. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 50 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

84. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 60 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

85. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 70 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

86. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 80 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

87. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 90 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

88. The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 100 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

89. The composition as recited in claim 57, wherein the composition is provided as a separate component of a kit.

90. A method of producing a liquid pharmaceutical composition comprising: combining the dosage form of claim 57 with an aqueous medium.

91. A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form as recited in claim 57 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

92. The method as recited in claim 91, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

93. The method as recited in claim 91, wherein the composition is administered once or twice a day.

94. A method for administering a liquid pharmaceutical composition to a subject, comprising: combining the pharmaceutical composition as recited in claim 57 with an aqueous medium to form a suspension, and orally administering the suspension to the subject in a single dose without administering an additional buffering agent.

95. The composition as recited in claim 1, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

96. The composition as recited in claim 95, wherein the proton pump inhibitor is omeprazole.

97. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 10 mg.

98. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 20 mg.

99. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 40 mg.

100. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 60 mg.

101. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 80 mg.

102. The composition as recited in claim 95, wherein the omeprazole is present in an amount of about 100 mg.

103. The composition as recited in claim 95, wherein the proton pump inhibitor is lansoprazole.

104. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 15 mg.

105. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 30 mg.

106. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 45 mg.

107. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 60 mg.

108. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 90 mg.

109. The composition as recited in claim 103, wherein the lansoprazole is present in an amount of about 100 mg.

110. The composition as recited in claim 1, wherein the proton pump inhibitor is micronized.

111. The composition as recited in claim 9, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

112. The composition as recited in claim 1, wherein the composition is provided as a separate component of a kit.

113. The composition of claim 1, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

114. The composition of claim 1, wherein the buffering agent comprises at least one of magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, or magnesium silicate.

115. The composition of claim 1, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, or other calcium salts.

116. The composition of claim 1, further comprising a disintegrant, flow aid, lubricant, adjuvant excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

117. The method of claim 24, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

118. The composition of claim 57, further comprising a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

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(12) **United States Patent**
Phillips

(10) **Patent No.: US 6,645,988 B2**
(45) **Date of Patent: *Nov. 11, 2003**

(54) **SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHOD OF USING SAME**

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This patent is subject to a terminal disclaimer.

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(57) **ABSTRACT**

The present invention relates to pharmaceutical preparations comprising substituted benzimidazole proton pump inhibitors. There is provided a liquid or solid pharmaceutical dosage form that is not enteric coated or delayed released containing a proton pump inhibitor and a Primary Essential Buffer. When the dosage form is placed in a liquid phase the Primary Essential Buffer maintains the pH of the environment at a value greater than the pKa of the proton pump inhibitor for a time sufficient to substantially avoid acid degradation of the proton pump inhibitor in the environment. Also provided is a method for treating acid-related gastrointestinal disorders by administering a solid pharmaceutical dosage form; and a kit for the preparation of a liquid oral pharmaceutical composition.

29 Claims, 3 Drawing Sheets

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FIG. 1

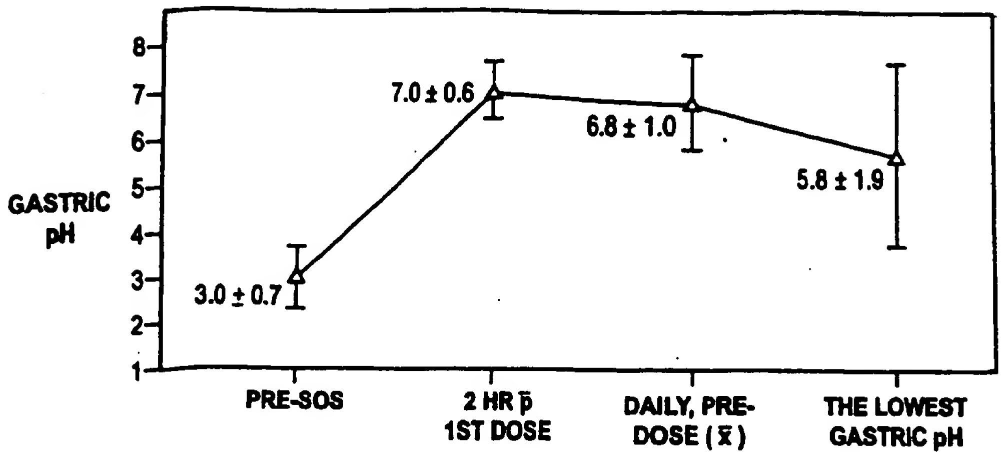

GASTRIC pH
8
7
6
5
4
3
2
1
3.0 ± 0.7
7.0 ± 0.6
6.8 ± 1.0
5.8 ± 1.9
PRE-SOS
2 HR p̄ 1ST DOSE
DAILY, PRE-DOSE (x̄)
THE LOWEST GASTRIC pH

FIG. 2

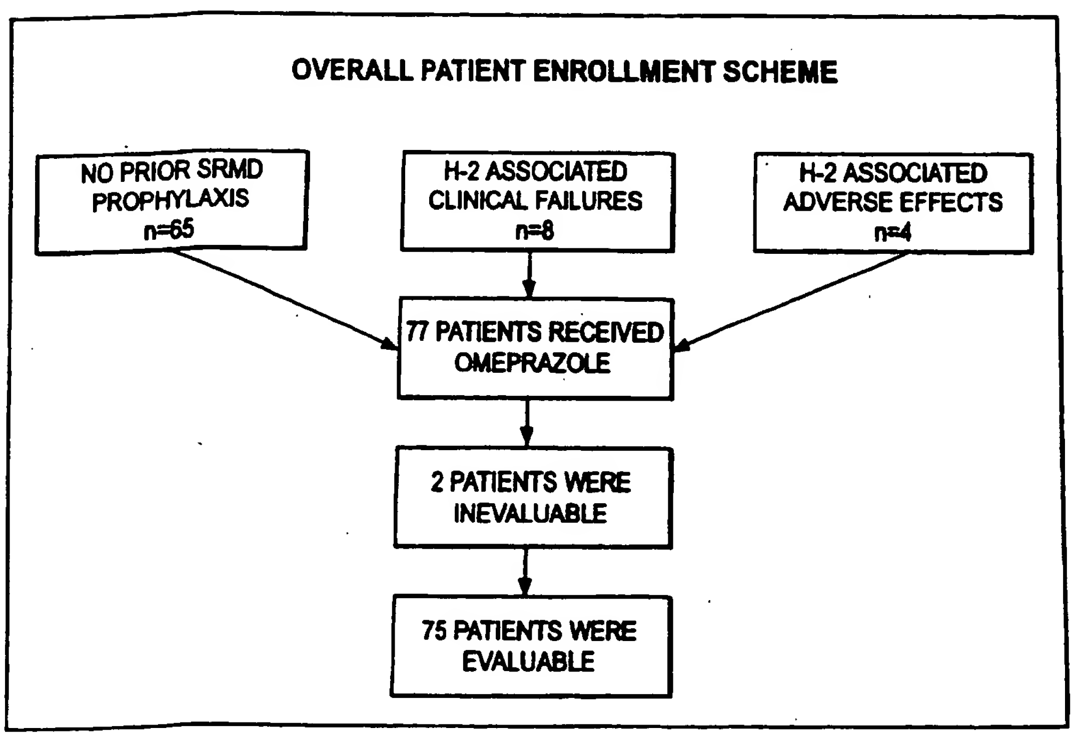

OVERALL PATIENT ENROLLMENT SCHEME
NO PRIOR SRMD PROPHYLAXIS n=65
H-2 ASSOCIATED CLINICAL FAILURES n=8
H-2 ASSOCIATED ADVERSE EFFECTS n=4
77 PATIENTS RECEIVED OMEPRAZOLE
2 PATIENTS WERE INEVALUABLE
75 PATIENTS WERE EVALUABLE

FIG. 3

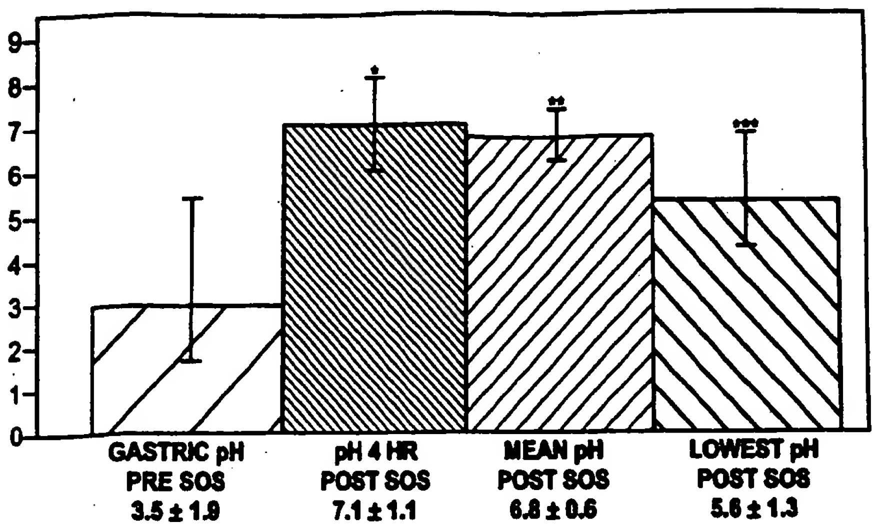

9
8
7
6
5
4
3
2
1
0
GASTRIC pH
PRE SOS
3.5 ± 1.9
pH 4 HR
POST SOS
7.1 ± 1.1
MEAN pH
POST SOS
6.8 ± 0.6
LOWEST pH
POST SOS
5.6 ± 1.3

FIG. 4

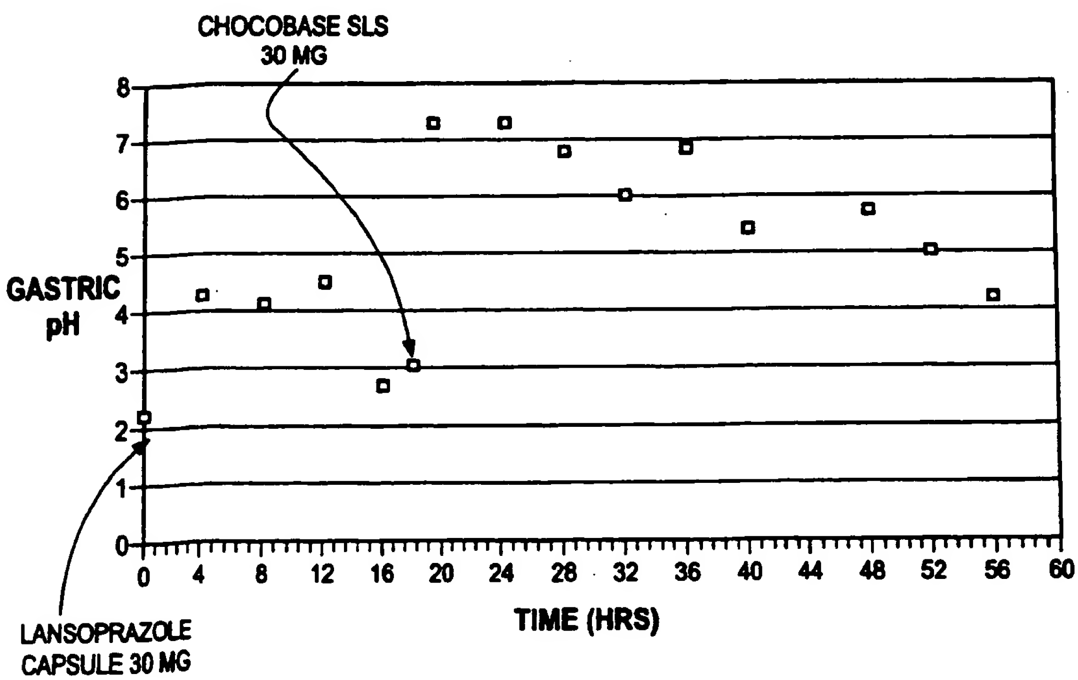
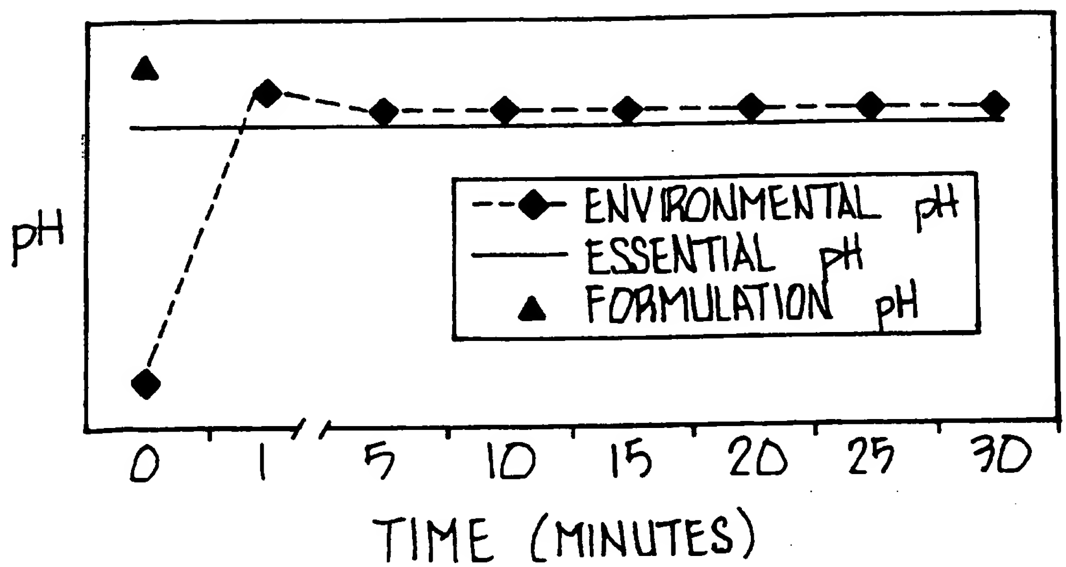

CHOCOBASE SLS
30 MG
GASTRIC
pH
8
7
6
5
4
3
2
1
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
TIME (HRS)
LANSOPRAZOLE
CAPSULE 30 MG

Fig. 5


pH
ENVIRONMENTAL pH
ESSENTIAL pH
FORMULATION pH
0
1
5
10
15
20
25
30
TIME (MINUTES)

SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHOD OF USING SAME

This application is a continuation-in-part of U.S. patent application Ser. No. 09/481,207 filed Jan. 11, 2000, now U.S. Pat. No. 6,489,346 which is a continuation-in-part of U.S. patent application Ser. No. 09/183,422 filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/680,376 filed on Jul. 15, 1996, now U.S. Pat. No. 5,840,737, which claims priority to U.S. Provisional Application Ser. No. 60/009,608 filed on Jan. 4, 1996. This application claims priority to all such previous applications, and such applications are hereby incorporated herein by reference to the extent permitted by law.

TECHNICAL FIELD

The present invention relates to pharmaceutical preparations comprising substituted benzimidazole proton pump inhibitors.

BACKGROUND OF THE INVENTION

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole, that inhibits gastric acid secretion. Omeprazole belongs to a class of antisecretory compounds called proton pump inhibitors ("PPIs") that do not exhibit anticholinergic or H_2 histamine antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H^+,K^+-ATPase enzyme system (proton pump) at the secretory surface of the gastric parietal cell.

Typically, omeprazole, lansoprazole and other proton pump inhibitors are formulated in an enteric-coated solid dosage form (as either a delayed-release capsule or tablet) or as an intravenous solution (as a product for reconstitution), and are prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. These above-listed conditions commonly arise in healthy or critically ill patients, and may be accompanied by significant upper gastrointestinal bleeding.

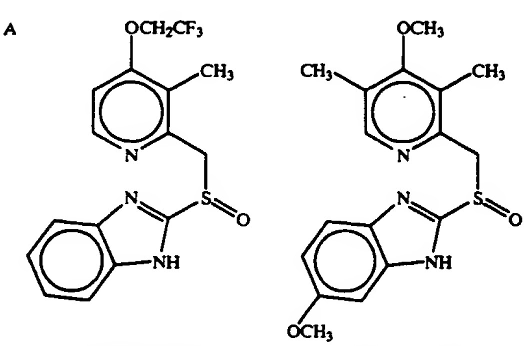
H_2-antagonists, antacids, and sucralfate are commonly administered to minimize the pain and the complications related to these conditions. These drugs have certain disadvantages associated with their use. Some of these drugs are not completely effective in the treatment of the aforementioned conditions and/or produce adverse side effects, such as mental confusion, constipation, diarrhea, and thrombocytopenia. H_2-antagonists, such as ranitidine and cimetidine, are relatively costly modes of therapy, particularly in NPO patients, which frequently require the use of automated infusion pumps for continuous intravenous infusion of the drug.

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, *Pathogenesis, Diagnosis and Treatment of Acute Gastric Mucosa Lesions*, Clin Gastroenterol 13: 635–650 (1984)). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., *The Prevention of Gastrointestinal Tract Bleeding in Patients in an Intensive Care Unit*, Surg. Gynecol. Obstet., 153: 214–220 (1981); Larson et al., *Gastric Response to Severe Head Injury*, Am. J. Surg. 147: 97–105 (1984); Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History*, N Engl. J. Med, 291: 925–929 (1974); Skillman et al., *Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated with Lethal Hemorrhage From Acute Stress Ulceration*, Am. J. Surg., 117: 523–530 (1969); and Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients*, N. Engl. J. Med., 330:377–381 (1994)). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients*, N. Engl. J. Med., 330:377–381 (1994)). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., *Continuous Intravenous cimetidine Decreases Stress-related Upper Gastro-intestinal Hemorrhage Without Promoting Pneumonia*, Crit. Care Med., 21: 19–39 (1993)). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History*, N Engl. J. Med, 291: 925–929 (1974); Peura and Johnson, *Cimetidine for Prevention and Treatment of Gastroduodenal Mucosal Lesions in Patients in an Intensive Care Unit*, Ann Intern Med., 103: 173–177 (1985)). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.

Omeprazole (Prilosec®), lansoprazole (Prevacid®) and other PPIs reduce gastric acid production by inhibiting H^+,K^+-ATPase of the parietal cell—the final common pathway for gastric acid secretion (Fellenius et al., *Substituted Benzimidazoles Inhibit Gastric Acid Secretion by Blocking H^+,K^+-ATPase*, Nature, 290:159–161(1981); Wallmark et al, *The Relationship Between Gastric Acid Secretion and Gastric H^+,K^+-ATPase Activity*, J. Biol.Chem., 260: 13681–13684 (1985); Fryklund et al., *Function and Structure of Parietal Cells After H^+,K^+-ATPase Blockade*, Am. J. Physiol., 254 (3 PT 1); G399–407 (1988)).

PPIs contain a sulfinyl group in a bridge between substituted benzimidazole and pyridine rings, as illustrated below.

A

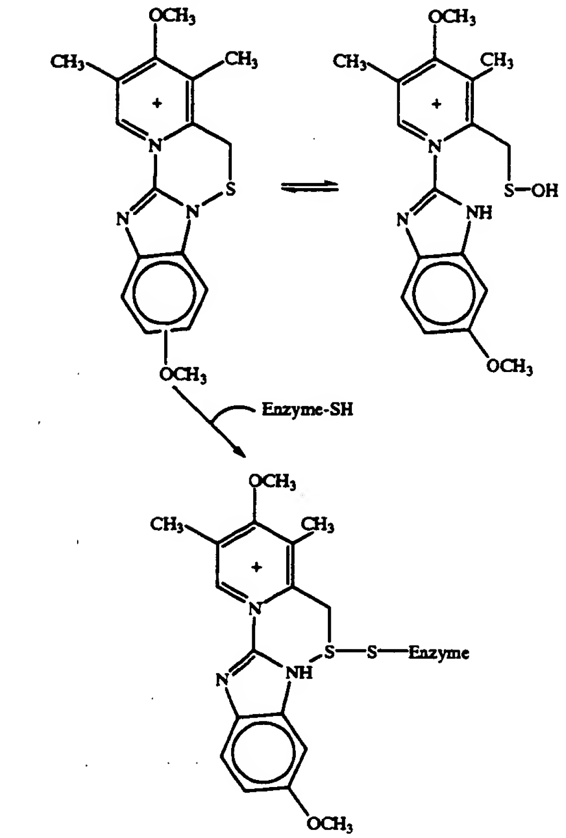


LANSOPRAZOLE OMEPRAZOLE

$\Updownarrow H^+$

-continued

B SULFENAMIDE SULFENIC ACID



ENZYME-INHIBITOR COMPLEX

At neutral pH, omeprazole, lansoprazole and other PPIs are chemically stable, lipid-soluble, weak bases that are devoid of inhibitory activity. These neutral weak bases reach parietal cells from the blood and diffuse into the secretory canaliculi, where the drugs become protonated and thereby trapped. The protonated agent rearranges to form a sulfenic acid and a sulfenamide. The sulfenamide interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane-spanning H^+,K^+-ATPase (Hardman et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, p. 907 (9^{th} ed. 1996)). Omeprazole and lansoprazole, therefore, are prodrugs that must be activated to be effective. The specificity of the effects of PPIs is also dependent upon: (a) the selective distribution of H^+,K^+-ATPase; (b) the requirement for acidic conditions to catalyze generation of the reactive inhibitor; and (c) the trapping of the protonated drug and the cationic sulfenamide within the acidic canaliculi and adjacent to the target enzyme. (Hardman et al., 1996).

Omeprazole and lansoprazole are available for oral administration as enteric-coated granules in gelatin capsules. Other proton pump inhibitors such as rabeprazole and pantoprazole are supplied as enteric-coated dosage forms. The enteric dosage forms of the prior art have been employed because they are acid labile; thus, it is important that these drugs not be exposed to low pH gastric acid prior to absorption. Although these drugs are stable at alkaline pH, they are destroyed rapidly as pH falls (e.g., by gastric acid). Therefore, if the micro-encapsulation or the enteric coating is disrupted (e.g., trituration to compound a liquid, or chewing the capsule), the dosage forms of the prior art will be exposed to degradation by the gastric acid in the stomach.

The absence of an intravenous or oral liquid dosage form in the United States has limited the testing and use of omeprazole, lansoprazole and rabeprazole in the critical care patient population. Barie et al., *Therapeutic Use of Omeprazole for Refractory Stress-induced Gastric Mucosal Hemorrhage*, Crit. Care Med., 20: 899–901 (1992) have described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multi-organ failure. However, such pellets are not ideal as they can aggregate and occlude such tubes, and they are not suitable for patients who cannot swallow the pellets. Am J. Health-Syst Pharm 56:2327–30 (1999).

Proton pump inhibitors such as omeprazole represent an advantageous alternative to the use of H_2-antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage. However, in their current form (capsules containing enteric-coated granules or enteric-coated tablets), proton pump inhibitors can be difficult or impossible to administer to patients who are either unwilling or unable to swallow tablets or capsules, such as critically ill patients, children, the elderly, and patients suffering from dysphagia. Therefore, it would be desirable to formulate a proton pump inhibitor solution or suspension which can be enterally delivered to a patient thereby providing the benefits of the proton pump inhibitor without the drawbacks of the current enteric-coated solid dosage forms.

Omeprazole, the first proton pump inhibitor introduced into use, has been formulated in many different embodiments such as in a mixture of polyethylene glycols, adeps solidus and sodium lauryl sulfate in a soluble, basic amino acid to yield a formulation designed for administration in the rectum as taught by U.S. Pat. No. 5,219,870 to Kim.

U.S. Pat. No. 5,395,323 to Berglund ('323) discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient. The '323 patent teaches the use of an omeprazole tablet which is placed in the device and dissolved by normal saline, and infused parenterally into the patient. This device and method of parenteral infusion of omeprazole does not provide the omeprazole solution as an enteral product, nor is this omeprazole solution directly administered to the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate antacid effect of the present formulation.

U.S. Pat. No. 4,786,505 to Lovgren et al. discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The core is then enterically coated. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH. The powder mixture is then formulated into enteric-coated small beads, pellets, tablets and may be loaded into capsules by conventional pharmaceutical procedures. This formulation of omeprazole does not teach a non-enteric-coated omeprazole dosage form which can be enterally administered to a patient who may be unable and/or unwilling to swallow capsules, tablets or pellets, nor does it teach a convenient form which can be used to make an omeprazole or other proton pump inhibitor solution or suspension.

Several buffered omeprazole oral solutions/suspensions have been disclosed. For example, Pilbrant et al., *Development of an Oral Formulation of Omeprazole*, Scand. J. Gastroent. 20(Suppl. 108): 113–120 (1985) teaches a suspension of micronized omeprazole, 60 mg, in 50 ml of water also containing 8 mmoles of sodium bicarbonate. The suspension was administered as follows: After fasting for at least 10 hours, patients were given a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later the patients took the omeprazole suspension and rinsed it down with another 50 ml of sodium bicarbonate solution. Ten (10), 20 and 30 minutes later, a further 50 ml of sodium bicarbonate solution was administered.

Andersson et el., *Pharmacokinetics of Various Single Intravenous and Oral Doses of Omeprazole*, Eur J. Clin. Pharmacol. 39: 195–197 (1990) discloses 10 mg, 40 mg, and 90 mg of oral omeprazole dissolved in PEG 400, sodium bicarbonate and water. The concentration of omeprazole cannot be determined, as volumes of diluent are not disclosed. Nevertheless, it is apparent from this reference that multiple doses of sodium bicarbonate were administered with and after the omeprazole suspension.

Andersson et al., *Pharmacokinetics and Bioavailability of Omeprazole After Single and Repeated Oral Administration in Healthy Subjects*, Br. J. Clin. Pharmac. 29: 557–63 (1990) teaches the oral use of 20 mg of omeprazole, which was dissolved in 20 g of PEG 400 (sp. gravity=1.14) and diluted with 50 ml of water containing 8 mmoles of sodium bicarbonate. In order to protect the omeprazole from gastric acid, the buffered solution was given with 48 mmoles of sodium bicarbonate in 300 ml of water.

Regardh et al., *The Pharmacokinetics of Omeprazole in Humans—A Study of Single Intravenous and Oral Doses*, Ther. Drug Mon. 12: 163–72 (1990) discloses an oral dose of omeprazole at a concentration 0.4 mg/ml after the drug was dissolved in PEG 400, water and sodium bicarbonate (8 mmoles). A solution containing 16 mmoles of sodium bicarbonate in 100 ml of water was concomitantly given with the omeprazole solution. That dose was followed by a solution of 50 ml of 0.16 mol/L sodium bicarbonate that was used for rinsing the vessel. In both the IV and oral experiment, 50 ml of 0.16 mol/L sodium bicarbonate was administered 5 minutes before administration, and 10, 20 and 30 minutes post-dose.

Landahl et al., *Pharmacokinetics Study of Omeprazole in Elderly Healthy Volunteers*, Clin. Pharmacokinetics 23 (6): 469–476 (1992) teaches the use of an oral dose of 40 mg of omeprazole dissolved in PEG 400, sodium bicarbonate and water. This reference does not disclose the final concentrations utilized. Again, this reference teaches the multiple administration of sodium bicarbonate (8 mmol/L and 16 mmol/L) after the omeprazole solution.

Andersson et al., *Pharmacokinetics of* [^{14}C] *Omeprazole in Patients with Liver Cirrhosis*, Clin. Pharmacokinetics 24(1): 71–78 (1993) discloses the oral administration of 40 mg of omeprazole, which was dissolved in PEG 400, water and sodium bicarbonate. This reference does not teach the final concentration of the omeprazole solution administered, although it emphasizes the need for pre, concomitant and post sodium bicarbonate dosing with a total of 48 mmoles to prevent acid degradation of the drug.

Nakagawa, et al., *Lansoprazole: Phase I Study of lansoprazole* (*AG*-1749) *Anti-ulcer Agent*, J. Clin. Therapeutics & Med.(1991) teaches the oral administration of 30 mg of lansoprazole suspended in 100 ml of sodium bicarbonate, which was administered to patients through a nasogastric tube.

All of the buffered omeprazole solutions described in these references were administered orally, and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration. In all of these studies, repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration. In the above-cited studies, as much as 48 mmoles of sodium bicarbonate in 300 ml of water must be ingested for a single dose of omeprazole to be orally administered.

The buffered omeprazole solutions of the above cited prior art require the ingestion of large amounts of sodium bicarbonate and large volumes of water by repeated administration. This has been considered necessary to prevent acid degradation of the omeprazole. In the above-cited studies, basically healthy volunteers, rather than sick patients, were given dilute buffered omeprazole utilizing pre-dosing and post-dosing with large volumes of sodium bicarbonate.

The administration of large amounts of sodium bicarbonate can produce at least six significant adverse effects, which can dramatically reduce the efficacy of the omeprazole in patients and reduce the overall health of the patients. First, the fluid volumes of these dosing protocols would not be suitable for sick or critically ill patients who must receive multiple doses of omeprazole. The large volumes would result in the distention of the stomach and increase the likelihood of complications in critically ill patients such as the aspiration of gastric contents.

Second, because bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their reflux disease as the belching can cause upward movement of stomach acid (Brunton, *Agents for the Control of Gastric Acidity and Treatment of Peptic Ulcers*, In, Goodman A G, et al. *The Pharmacologic Basis of Therapeutics*. (New York, p. 907 (1990)).

Third, patients with conditions such as hypertension or heart failure are standardly advised to avoid the intake of excessive sodium as it can cause aggravation or exacerbation of their hypertensive conditions (Brunton, supra). The ingestion of large amounts of sodium bicarbonate is inconsistent with this advice.

Fourth, patients with numerous conditions that typically accompany critical illness should avoid the intake of excessive sodium bicarbonate as it can cause metabolic alkalosis that can result in a serious worsening of the patient's condition.

Fifth, excessive antacid intake (such as sodium bicarbonate) can result in drug interactions that produce serious adverse effects. For example, by altering gastric and urinary pH, antacids can alter rates of drug dissolution and absorption, bioavailability, and renal elimination (Brunton, supra).

Sixth, because the buffered omeprazole solutions of the prior art require prolonged administration of sodium bicarbonate, it makes it difficult for patients to comply with the regimens of the prior art. For example, Pilbrant et al. disclose an oral omeprazole administration protocol calling for the administration to a subject who has been fasting for at least ten hours, a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later, the subject ingests a suspension of 60 mg of omeprazole in 50 ml of

water that also contains 8 mmoles of sodium bicarbonate. This is rinsed down with another 50 ml of 8 mmoles sodium bicarbonate solution. Ten minutes after the ingestion of the omeprazole dose, the subject ingests 50 ml of bicarbonate solution (8 mmoles). This is repeated at twenty minutes and thirty minutes post omeprazole dosing to yield a total of 48 mmoles of sodium bicarbonate and 300 ml of water in total that are ingested by the subject for a single omeprazole dose. Not only does this regimen require the ingestion of excessive amounts of bicarbonate and water, which is likely to be dangerous to some patients, it is unlikely that even healthy patients would comply with this regimen.

It is well documented that patients who are required to follow complex schedules for drug administration are non-compliant and, thus, the efficacy of the buffered omeprazole solutions of the prior art would be expected to be reduced due to non-compliance. Compliance has been found to be markedly reduced when patients are required to deviate from a schedule of one or two (usually morning and night) doses of a medication per day. The use of the prior art buffered omeprazole solutions which require administration protocols with numerous steps, different drugs (sodium bicarbonate+omeprazole+PEG 400 versus sodium bicarbonate alone), and specific time allotments between each stage of the total omeprazole regimen in order to achieve efficacious results is clearly in contrast with both current drug compliance theories and human nature.

The prior art (Pilbrant et al., 1985) teaches that the buffered omeprazole suspension can be stored at refrigerator temperatures for a week and deep frozen for a year while still maintaining 99% of its initial potency. It would be desirable to have an omeprazole or other proton pump inhibitor solution or suspension that could be stored at room temperature or in a refrigerator for periods of time which exceed those of the prior art while still maintaining 99% of the initial potency. Additionally, it would be advantageous to have a form of the omeprazole and bicarbonate which can be utilized to instantly make the omeprazole solution/suspension of the present invention which is supplied in a solid form which imparts the advantages of improved shelf-life at room temperature, lower cost to produce, less expensive shipping costs, and which is less expensive to store.

It would, therefore, be desirable to have a proton pump inhibitor formulation, which provides a cost-effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonists, antacids, and sucralfate. Further, it would be desirable to have a proton pump inhibitor formulation which is convenient to prepare and administer to patients unable to ingest solid dosage forms such as tablets or capsules, which is rapidly absorbed, and can be orally or enterally delivered as a liquid form or solid form. It is desirable that the liquid formulation not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an antacid immediately upon delivery.

It would further be advantageous to have a potentiator or enhancer of the pharmacological activity of the PPIs. It has been theorized by applicant that the PPIs can only exert their effects on H^+,K^+-ATPase when the parietal cells are active. Accordingly, applicant has identified, as discussed below, parietal cell activators that are administered to synergistically enhance the activity of the PPIs.

Additionally, the intravenous dosage forms of PPIs of the prior art are often administered in larger doses than the oral forms. For example, the typical adult IV dose of omeprazole is greater than 100 mg/day whereas the adult oral dose is 20 to 40 mg/day. Large IV doses are necessary to achieve the desired pharmacologic effect because, it is believed, many of the parietal cells are in a resting phase (mostly inactive) during an IV dose given to patients who are not taking oral substances by mouth (npo) and, therefore, there is little active (that which is inserted into the secretory canalicular membrane) H^+,K^+-ATPase to inhibit. Because of the clear disparity in the amount of drug necessary for IV versus oral doses, it would be very advantageous to have compositions and methods for IV administration where significantly less drug is required.

SUMMARY OF THE INVENTION AND ADVANTAGES

The foregoing advantages and objects are accomplished by the present invention. The present invention provides an oral solution/suspension comprising a proton pump inhibitor and at least one buffering agent. The PPI can be any substituted benzimidazole compound having H^+,K^+-ATPase inhibiting activity and being unstable to acid. The inventive composition can alternatively be formulated as a powder, tablet, suspension tablet, chewable tablet, capsule, two-part tablet or capsule, effervescent powder, effervescent tablet, pellets and granules. Such dosage forms are advantageously devoid of any enteric coating or delayed or sustained-release delivery mechanisms, and comprise a PPI and at least one buffering agent to protect the PPI against acid degradation. Both the liquid and dry dosage forms can further include anti-foaming agents, parietal cell activators and flavoring agents.

In another embodiment, oral dosage forms are disclosed comprising a combination of enteric-coated or delayed-released PPI with an antacid(s). Such forms may optionally comprise non-enteric-coated PPI.

Kits utilizing the inventive dry dosage forms are also disclosed herein to provide for the easy preparation of a liquid composition from the dry forms.

In accordance with the present invention, there is further provided a method of treating gastric acid disorders by orally administering to a patient a pharmaceutical composition(s) and/or dosage form(s) disclosed herein.

Additionally, the present invention relates to a method for enhancing the pharmacological activity of an intravenously administered proton pump inhibitor in which at least one parietal cell activator is orally administered to the patient before, during and/or after the intravenous administration of the proton pump inhibitor.

Finally, the present invention relates to a method for optimizing the type and amount of buffer desirable for individual PPIs.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

FIG. 1 is a graph showing the effect of the omeprazole solution of the present invention on gastric pH in patients at risk for upper gastrointestinal bleeding from stress-related mucosal damage;

FIG. 2 is a flow chart illustrating a patient enrollment scheme;

FIG. 3 is a bar graph illustrating gastric pH both pre- and post-administration of omeprazole solution according to the present invention;

FIG. 4 is a graph illustrating the stomach pH values after the oral administration of both ChocoBase plus lansoprazole and lansoprazole alone;

FIG. 5 is a graph illustrating a pH probe confirmation of GERD;

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

In general, the present invention relates to a pharmaceutical composition comprising a proton pump inhibitor and a buffering agent with or without one or more parietal cell activators, and which is not enteric coated, sustained or delayed-release. While the present invention may be embodied in many different forms, several specific embodiments are discussed herein with the understanding that the present disclosure is to be considered only as an exemplification of the principles of the invention, and it is not intended to limit the invention to the embodiments illustrated.

For the purposes of this application, the term "proton pump inhibitor" (or "PPI") shall mean any substituted benzimidazole possessing pharmacological activity as an inhibitor of H^+,K^+-ATPase, including, but not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, and leminoprazole. The definition of "PPI" also means that the active agents of the present invention may be administered, if desired, in the form of salts, esters, amides, enantiomers, isomers, tautomers, prodrugs, derivatives and the like, provided the salt, ester, amide, enantiomer, isomer, tautomer, prodrug, or derivative is suitable pharmacologically, that is, effective in the present methods, combinations and compositions. Salts, esters, amides, enantiomers, isomers, tautomers, prodrugs and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 4th Ed. (New York: Wiley-Interscience, 1992).

The therapeutic agents of the present invention can be formulated as a single pharmaceutical composition or as independent multiple pharmaceutical dosage forms. Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, buccal (for example, sublingual), or parenteral (for example, intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used.

As explained further herein, the PPIs generally inhibit ATPase in the same way. Differences in onset and relative potencies are largely due to differences in the acid instability of the parent compounds.

The inventive composition comprises dry formulations, solutions and/or suspensions of the proton pump inhibitors. As used herein, the terms "suspension" and "solution" are interchangeable with each other and mean solutions and/or suspensions of the substituted benzimidazoles.

After absorption of the PPI (or administration intravenously) the drug is delivered via the bloodstream to various tissues and cells of the body including the parietal cells. Not intending to be bound by any one theory, research suggests that when PPI is in the form of a weak base and is non-ionized, it freely passes through physiologic membranes, including the cellular membranes of the parietal cell. It is believed that the non-ionized PPI moves into the acid-secreting portion of the parietal cell, the secretory canaliculus. Once in the acidic milieu of the secretory canaliculus, the PPI is apparently protonated (ionized) and converted to the active form of the drug. Generally, ionized proton pump inhibitors are membrane impermeable and form disulfide covalent bonds with cysteine residues in the alpha subunit of the proton pump. Such active forms are included within the definition of "PPI" herein.

The inventive pharmaceutical composition comprising a proton pump inhibitor such as omeprazole, lansoprazole or other proton pump inhibitor and derivatives thereof can be used for the treatment or prevention of gastrointestinal conditions including, but not limited to, active duodenal ulcers, gastric ulcers, dyspepsia, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, and pathological hypersecretory conditions such as Zollinger Ellison Syndrome. Treatment of these conditions is accomplished by administering to a patient an effective amount of the pharmaceutical composition according to the present invention.

The proton pump inhibitor is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. The term "effective amount" means, consistent with considerations known in the art, the amount of PPI or other agent effective to achieve a pharmacologic effect or therapeutic improvement without undue adverse side effects, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood transfusion, improved survival rate, more rapid recovery, parietal cell activation and H^+,K^+-ATPase inhibition or improvement or elimination of symptoms, and other indicators as are selected as appropriate measures by those skilled in the art.

The dosage range of omeprazole or other proton pump inhibitors can range from less than approximately 2 mg/day to approximately 300 mg/day. For example, the standard approximate adult daily oral dosage is typically 20 mg of omeprazole, 30 mg lansoprazole, 40 mg pantoprazole, 20 mg rabeprazole, 20 mg esomeprazole, and the pharmacologically equivalent doses of pariprazole and leminoprazole.

A pharmaceutical formulation of the proton pump inhibitors utilized in the present invention can be administered orally or enterally to the patient. This can be accomplished, for example, by administering the solution via a nasogastric (ng) tube or other indwelling tubes placed in the GI tract. In order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the PPI solution of the present invention is administered in a single dose which does not require any further administration of bicarbonate, or other buffer following the administration of the PPI solution, nor does it require a large amount of bicarbonate or buffer in total. That is, unlike the prior art PPI solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose, which does not require administration of bicarbonate either before or after administration of the PPI. The present invention eliminates the need to pre- or post-dose with additional volumes of water and sodium bicarbonate. The amount of bicarbonate administered via the single dose administration of the present invention is less than the amount of bicarbonate administered as taught in the prior art references cited above.

II. Preparation of Oral Liquids

As described in Phillips U.S. Pat. No. 5,840,737, the liquid oral pharmaceutical composition of the present invention is prepared by mixing omeprazole enteric-coated gran-

ules (Prilosec® AstraZeneca), or omeprazole base, or other proton pump inhibitor or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). In one embodiment, omeprazole or other proton pump inhibitor, which can be obtained from powder, capsules, and tablets or obtained from the solution for parenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other PPI) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0 mg/ml. The preferred concentration for the omeprazole in the solution ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml, with 2.0 mg/ml being the standard concentration. For lansoprazole (Prevacid® TAP Pharmaceuticals, Inc.) the concentration can range from about 0.3 mg/ml to 10 mg/ml with the preferred concentration being about 3 mg/ml.

Although sodium bicarbonate is the preferred buffering agent to protect the PPIs against acid degradation, many other weak and strong bases (and mixtures thereof) can be utilized. For the purposes of this application, "buffering agent" or "buffer" shall mean any pharmaceutically appropriate weak base or strong base (and mixtures thereof) that, when formulated or delivered with (e.g., before, during and/or after) the PPI, functions to substantially prevent or inhibit the acid degradation of the PPI by gastric acid sufficient to preserve the bioavailability of the PPI administered. The buffering agent is administered in an amount sufficient to substantially achieve the above functionality. Therefore, the buffering agent of the present invention, when in the presence of gastric acid, must only elevate the pH of the stomach sufficiently to achieve adequate bioavailability of the drug to effect therapeutic action.

Accordingly, examples of buffering agents include, but are not limited to, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, other magnesium salts, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate coprecipitate, a mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium cholride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts.

The pharmaceutically acceptable carrier of the oral liquid may comprise a bicarbonate salt of Group IA metal as buffering agent, and can be prepared by mixing the bicarbonate salt of the Group IA metal, preferably sodium bicarbonate, with water. The concentration of the bicarbonate salt of the Group IA metal in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. In one embodiment, the content of the bicarbonate salt of the Group IA metal ranges from about 3 mEq to about 45 mEq per oral dose.

In another embodiment, the amount of sodium bicarbonate 8.4% used in the solution of the present invention is approximately 1 mEq (or mmole) sodium bicarbonate per 2 mg omeprazole, with a range of approximately 0.2 mEq (mmole) to 5 mEq (mmole) per 2 mg of omeprazole.

In an embodiment of the present invention, enterically-coated omeprazole particles are obtained from delayed release capsules (Prilosec® AstraZeneca). Alternatively, omeprazole base powder can be used. The enterically coated omeprazole particles are mixed with a sodium bicarbonate ($NaHCO_3$) solution (8.4%), which dissolves the enteric coating and forms an omeprazole solution.

The inventive solutions and other dosage forms of the present invention have pharmacokinetic advantages over standard enteric-coated and time-released PPI dosage forms, including: (a) more rapid drug absorbance time (about 10 to 60 minutes) following administration for the PPI solution or dry form versus about 1 to 3 hours following administration for the enteric-coated pellets; (b) the buffer solution protects the PPI from acid degradation prior to absorption; (c) the buffer acts as an antacid while the PPI is being absorbed for rapid antacid relief; and (d) the solutions can be administered through an existing indwelling tube without clogging, for example, nasogastric or other feeding tubes (jejunal or duodenal), including small bore needle catheter feeding tubes.

Solutions, suspensions and powders for reconstitutable delivery systems include vehicles such as suspending agents (for example, gums, xanthans, cellulosics and sugars), humectants (for example, sorbitol), solubilizers (for example, ethanol, water, PEG and propylene glycol), surfactants (for example, sodium lauryl sulfate, Spans, Tweens, and cetyl pyridine), preservatives and antioxidants (for example, parabens, vitamins E and C, and ascorbic acid), anti-caking agents, coating agents, and chelating agents (for example, EDTA).

Additionally, various additives can be incorporated into the inventive solution to enhance its stability, sterility and isotonicity. Antimicrobial preservatives, such as ambicin, antioxidants, chelating agents, and additional buffers can be added. However, microbiological evidence shows that this formulation inherently possesses antimicrobial and antifungal activity. Various antibacterial and antifungal agents such as, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like can enhance prevention of the action of microorganisms.

In many cases, it would be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Additionally, thickening agents such as methyl cellulose are desirable to use in order to reduce the settling of the omeprazole or other PPI or derivatives thereof from the suspension.

The liquid oral solution may further comprise flavoring agents (e.g., chocolate, thalmantin, aspartame, root beer or watermelon) or other flavorings stable at pH 7 to 9, anti-foaming agents (e.g., simethicone 80 mg, Mylicon®) and parietal cell activators (discussed below).

The present invention further includes a pharmaceutical composition comprising omeprazole or other proton pump inhibitor and derivatives thereof and at least one buffering agent in a form convenient for storage, whereby when the composition is placed into an aqueous solution, the composition dissolves and/or disperses yielding a suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution or suspension in an aqueous solution. The omeprazole or other PPIs and buffering agent can be formed into a tablet, capsule, pellets or granules, by methods well known to those skilled in the art.

The resultant omeprazole solution is stable at room temperature for several weeks and inhibits the growth of bac-

teria or fungi as shown in Example [illegible] below. Indeed, as established in Example XIII, the solution maintains greater than 90% of its potency for 12 months. By providing a pharmaceutical composition including omeprazole or other PPI with buffer in a solid form, which can be later dissolved or suspended in a prescribed amount of aqueous solution to yield the desired concentration of omeprazole and buffer, the cost of production, shipping, and storage are greatly reduced as no liquids are shipped (reducing weight and cost), and there is no need to refrigerate the solid form of the composition or the solution. Once mixed the resultant solution can then be used to provide dosages for a single patient over a course of time, or for several patients.

III. Tablets and Other Solid Dosage Forms

As mentioned above, and as described in part in Phillips U.S. Pat. No. 5,840,737, the formulations of the present invention can also be manufactured in concentrated forms, such as powders, capsules, tablets, suspension tablets and effervescent tablets or powders, which can be swallowed whole or first dissolved such that upon reaction with water, gastric secretions or other diluent, the aqueous form of the present invention is produced.

The present pharmaceutical tablets or other solid dosage forms disintegrate rapidly in aqueous media and form an aqueous solution of the PPI and buffering agent with minimal shaking or agitation. Such tablets utilize commonly available materials and achieve these and other desirable objectives. The tablets or other solid dosage forms of this invention provide for precise dosing of a PPI that may be of low solubility in water. They may be particularly useful for medicating children and the elderly and others in a way that is much more acceptable than swallowing or chewing a tablet. The tablets that are produced have low friability, making them easily transportable.

The term "suspension tablets" as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the PPI. The suspension tablets of this invention comprise, in combination, a therapeutic amount of a PPI, a buffering agent, and a disintegrant. More particularly, the suspension tablets comprise about 20 mg omeprazole and about 4–30 mEq of sodium bicarbonate.

Croscarmellose sodium is a known disintegrant for tablet formulations, and is available from FMC Corporation, Philadelphia, Pa. under the trademark Ac-Di-Sol®. It is frequently blended in compressed tableting formulations either alone or in combination with microcrystalline cellulose to achieve rapid disintegration of the tablet.

Microcrystalline cellulose, alone or co processed with other ingredients, is also a common additive for compressed tablets and is well known for its ability to improve compressibility of difficult to compress tablet materials. It is commercially available under the Avicel® trademark. Two different Avicel® products are utilized, Avicel® PH which is microcrystalline cellulose, and Avicel® AC-815, a co processed spray dried residue of microcrystalline cellulose and a calcium-sodium alginate complex in which the calcium to sodium ratio is in the range of about 0.40:1 to about 2.5:1. While AC-815 is comprised of 85% microcrystalline cellulose (MCC) and 15% of a calcium-sodium alginate complex, for purposes of the present invention this ratio may be varied from about 75% MCC to 25% alginate up to about 95% MCC to 5% alginate. Depending on the particular formulation and active ingredient, these two components may be present in approximately equal amounts or in unequal amounts, and either may comprise from about 10% to about 50% by weight of the tablet.

The suspension tablet composition may, in addition to the ingredients described above, contain other ingredients often used in pharmaceutical tablets, including flavoring agents, sweetening agents, flow aids, lubricants or other common tablet adjuvants, as will be apparent to those skilled in the art. Other disintegrants, such as crospovidone and sodium starch glycolate may be employed, although croscarmellose sodium is preferred.

In addition to the suspension tablet, the solid formulation of the present invention can be in the form of a powder, a tablet, a capsule, or other suitable solid dosage form (e.g., a pelleted form or an effervescing tablet, troche or powder), which creates the inventive solution in the presence of diluent or upon ingestion. For example, the water in the stomach secretions or water, which is used to swallow the solid dosage form, can serve as the aqueous diluent.

Compressed tablets are solid dosage forms prepared by compacting a formulation containing an active ingredient and excipients selected to aid the processing and improve the properties of the product. The term "compressed tablet" generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression or by pre-compaction tapping followed by a final compression.

Dry oral formulations can contain excipients such as binders (for example, hydroxypropylmethylcellulose, polyvinyl pyrilodone, other cellulosic materials and starch), diluents (for example, lactose and other sugars, starch, dicalcium phosphate and cellulosic materials), disintegrating agents (for example, starch polymers and cellulosic materials) and lubricating agents (for example, stearates and talc).

Such solid forms can be manufactured as is well known in the art. Tablet forms can include, for example, one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmaceutically compatible carriers. The manufacturing processes may employ one, or a combination of, four established methods: (1) dry mixing; (2) direct compression; (3) milling; and (4) non-aqueous granulation. Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Such tablets may also comprise film coatings, which preferably dissolve upon oral ingestion or upon contact with diluent.

Non-limiting examples of buffering agents which could be utilized in such tablets include sodium bicarbonate, alkali earth metal salts such as calcium carbonate, calcium hydroxide, calcium lactate, calcium glycerophosphate, calcium acetate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide. A particular alkali earth metal salt useful for making an antacid tablet is calcium carbonate.

An example of a low density alkali earth metal salt useful for making the granules according to the present invention is extra light calcium carbonate available from Specialty Minerals Inc., Adams, Me. The density of the extra light calcium carbonate, prior to being processed according to the present invention, is about 0.37 g/ml. Other acceptable buffers are provided throughout this application.

The granules used to make the tablets according to one embodiment of the present invention are made by either spray drying or pre-compacting the raw materials. Prior to being processed into granules by either process, the density of the alkali earth metal salts useful in the present invention

ranges from about 0.3 g/ml to about 0.55 g/ml, preferably about 0.35 g/ml to about 0.45 g/ml, even more preferably about 0.37 g/ml to about 0.42 g/ml.

Additionally, the present invention can be manufactured by utilizing micronized compounds in place of the granules or powder. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate. Although micronization results in increased surface area possibly causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole and other proton pump inhibitors.

The present invention also relates to administration kits to ease mixing and administration. A month's supply of powder or tablets, for example, can be packaged with a separate month's supply of diluent, and a re-usable plastic dosing cup. More specifically, the package could contain thirty (30) suspension tablets containing 20 mg omeprazole each, 1 L sodium bicarbonate 8.4% solution, and a 30 ml dose cup. The user places the tablet in the empty dose cup, fills it to the 30 ml mark with the sodium bicarbonate, waits for it to dissolve (gentle stirring or agitation may be used), and then ingests the suspension. One skilled in the art will appreciate that such kits may contain many different variations of the above components. For example, if the tablets or powder are compounded to contain PPI and buffering agent, the diluent may be water, sodium bicarbonate, or other compatible diluent, and the dose cup can be larger or smaller than 30 ml in size. Also, such kits can be packaged in unit dose form, or as weekly, monthly, or yearly kits, etc.

Although the tablets of this invention are primarily intended as a suspension dosage form, the granulations used to form the tablet may also be used to form rapidly disintegrating chewable tablets, lozenges, troches, or swallowable tablets. Therefore, the intermediate formulations as well as the process for preparing them provide additional novel aspects of the present invention.

Effervescent tablets and powders are also prepared in accordance with the present invention. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and tartaric acid. When the salts are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence."

The choice of ingredients for effervescent granules depends both upon the requirements of the manufacturing process and the necessity of making a preparation which dissolves readily in water. The two required ingredients are at least one acid and at least one base. The base releases carbon dioxide upon reaction with the acid. Examples of such acids include, but are not limited to, tartaric acid and citric acid. Preferably, the acid is a combination of both tartaric acid and citric acid. Examples of bases include, but are not limited to, sodium carbonate, potassium bicarbonate and sodium bicarbonate. Preferably, the base is sodium bicarbonate, and the effervescent combination has a pH of about 6.0 or higher.

Effervescent salts preferably include the following ingredients, which actually produce the effervescence: sodium bicarbonate, citric acid and tartaric acid. When added to water the acids and base react to liberate carbon dioxide, resulting in effervescence. It should be noted that any acid-base combination which results in the liberation of carbon dioxide could be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use, and result in a pH of about 6.0 or higher.

It should be noted that it requires 3 molecules of $NaHCO_3$ to neutralize 1 molecule of citric acid and 2 molecules of $NaHCO_3$ to neutralize 1 molecule of tartaric acid. It is desired that the approximate ratio of ingredients is as follows:

Citric Acid:Tartaric Acid:Sodium Bicarbonate=1:2:3.44 (by weight). This ratio can be varied and continue to produce an effective release of carbon dioxide. For example, ratios of about 1:0:3 or 0:1:2 are also effective.

The method of preparation of the effervescent granules of the present invention employs three basic processes: wet and dry granulation, and fusion. The fusion method is used for the preparation of most commercial effervescent powders. It should be noted that although these methods are intended for the preparation of granules, the formulations of effervescent salts of the present invention could also be prepared as tablets, according to well known prior art technology for tablet preparation.

Wet granulation is the oldest method of granule preparation. The individual steps in the wet granulation process of tablet preparation include milling and sieving of the ingredients; dry powder mixing; wet massing; granulation; and final grinding.

Dry granulation involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty rotary tablet press. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillation granulator. The individual steps include mixing of the powders; compressing (slugging); and grinding (slug reduction or granulation). No wet binder or moisture is involved in any of the steps.

The fusion method is the most preferred method for preparing the granules of the present invention. In this method, the compressing (slugging) step of the dry granulation process is eliminated. Instead, the powders are heated in an oven or other suitable source of heat.

IV. PPIs Administered with Parietal Cell Activators

Applicant has unexpectedly discovered that certain compounds, such as chocolate, calcium and sodium bicarbonate and other alkaline substances, stimulate the parietal cells and enhance the pharmacologic activity of the PPI administered. For the purposes of this application, "parietal cell activator" or "activator" shall mean any compound or mixture of compounds possessing such stimulatory effect including, but not limited to, chocolate, sodium bicarbonate, calcium (e.g., calcium carbonate, calcium gluconate, calcium hydroxide, calcium acetate and calcium glycerophosphate), peppermint oil, spearmint oil, coffee, tea and colas (even if decaffeinated), caffeine, theophylline, theobromine, and amino acids (particularly aromatic amino acids such as phenylalanine and tryptophan) and combinations thereof, and the salts thereof.

Such parietal cell activators are administered in an amount sufficient to produce the desired stimulatory effect without causing untoward side effects to patients. For example, chocolate, as raw cocoa, is administered in an amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of other PPI). The dose of activator administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response (i.e., enhanced

effect of PPI) over a reasonable time frame. The dose will be determined by the strength of the particular compositions employed and the condition of the person, as well as the body weight of the person to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular composition.

The approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other PPI) are:

Chocolate (raw cocoa)—5 mg to 2.5 g
Sodium bicarbonate—7 mEq to 25 mEq
Calcium carbonate—1 mg to 1.5 g
Calcium gluconate—1 mg to 1.5 g
Calcium lactate—1 mg to 1.5 g
Calcium hydroxide—1 mg to 1.5 g
Calcium acetate—0.5 mg to 1.5 g
Calcium glycerophosphate—0.5 mg to 1.5 g
Peppermint oil—(powdered form) 1 mg to 1 g
Spearmint oil—(powdered form) 1 mg to 1 g
Coffee—20 ml to 240 ml
Tea—20 ml to 240 ml
Cola—20 ml to 240 ml
Caffeine—0.5 mg to 1.5 g
Theophylline—0.5 mg to 1.5 g
Theobromine—0.5 mg to 1.5 g
Phenylalanine—0.5 mg to 1.5 g
Tryptophan—0.5 mg to 1.5 g

Pharmaceutically acceptable carriers are well-known to those who are skilled in the art. The choice of carrier will be determined, in part, both by the particular composition and by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical compositions of the present invention.

V. EXAMPLES

The present invention is further illustrated by the following formulations, which should not be construed as limiting in any way. The practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmacology and pharmaceutics, which are within the skill of the art.

Example 1

A. Fast Disintegrating Suspension Tablets of Omeprazole

A fast disintegrating tablet is compounded as follows: Croscarmellose sodium 300 g is added to the vortex of a rapidly stirred beaker containing 3.0 kg of deionized water. This slurry is mixed for 10 minutes. Omeprazole 90 g (powdered) is placed in the bowl of a Hobart mixer. After mixing, the slurry of croscarmellose sodium is added slowly to the omeprazole in the mixer bowl, forming a granulation, which is then placed in trays and dried at 70° C. for three hours. The dry granulation is then placed in a blender, and to it is added 1,500 g of Avicel® AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 1,500 g of Avicel® PH-302 (microcrystalline cellulose). After this mixture is thoroughly blended, 35 g of magnesium stearate is added and mixed for 5 minutes. The resulting mixture is compressed into tablets on a standard tablet press (Hata HS). These tablets have an average weight of about 0.75 g, and contain about 20 mg omeprazole. These tablets have low friability and rapid disintegration time. This formulation may be dissolved in an aqueous solution containing a buffering agent for immediate oral administration.

Alternatively, the suspension tablet may be swallowed whole with a solution of buffering agent. In both cases, the preferred solution is sodium bicarbonate 8.4%. As a further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other PPI) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole with an aqueous diluent.

B1. 10 mg Tablet Formula.	
Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg
B2. 10 mg Tablet Formula.	
PPI: one of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Other PPI in an equipotent amount	
Calcium lactate	375 mg
Calcium glycerophosphate	375 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg

-continued

Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg
B3. 10 mg Tablet Formula.	
PPI: one of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Other PPI in an equipotent amount	
Sodium bicarbonate	750 mg
Aspartame sodium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg
C1. 20 mg Tablet Formula.	
Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Calcium hydroxide	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg
C2. 20 mg Tablet Formula.	
PPI: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Other PPI in an equipotent amount	
Calcium lactate	375 mg
Calcium glycerophosphate	375 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg
C3. 20 mg Tablet Formula.	
PPI: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Other PPI in an equipotent amount	
Sodium bicarbonate	750 mg
Aspartame sodium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg

-continued

D1. Tablet for Rapid Dissolution.	
Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Croscarmellose sodium	12 mg
D2. Tablet for Rapid Dissolution. PPI: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg
Other PPI in an equipotent amount	
Calcium lactate	300 mg
Calcium glycerophosphate	300 mg
Calcium hydroxide	50 mg
Croscarmellose sodium	12 mg
D3. Tablet for Rapid Dissolution. PPI: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg
Other PPI in an equipotent amount	
Sodium bicarbonate	700 mg
Trisodium phosphate dodecahydrate	100 mg
Croscarmellose sodium	12 mg
E1. Powder for Reconstitution for Oral Use (or per ng tube).	
Omeprazole	20 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Glycerine	200 mg
E2. Powder for Reconstitution for Oral Use (or per ng tube). PPI: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg
Other PPI in an equipotent amount	
Calcium lactate	300 mg
Calcium glycerophosphate	300 mg
Calcium hydroxide	50 mg
Glycerine	200 mg
E3. Powder for Reconstitution for Oral Use (or per ng tube). PPI: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg
Other PPI in an equipotent amount	
Sodium bicarbonate	850 mg
Trisodium phosphate	50 mg
F1. 10 mg Tablet Formula.	
Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	175 mg

-continued

Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	1 mg
Magnesium stearate	1 mg
F2. 10 mg Tablet Formula..	
PPI: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other PPI in an equipotent amount	
Calcium lactate	475 mg
Calcium glycerophosphate	250 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	10 mg
Magnesium stearate	10 mg
F3. 10 mg Tablet Formula.	
PPI: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other PPI in an equipotent amount	
Sodium bicarbonate	700 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	10 mg
Magnesium stearate	10 mg
G1. 10 mg Tablet Formula.	
Omeprazole	10 mg (or lansoprazole or pantoprazole or other PPI in an equipotent amount)
Calcium lactate	200 mg
Calcium glycerophosphate	200 mg
Sodium bicarbonate	400 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg
G2. 10 mg Tablet Formula.	
PPI: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other PPI in an equipotent amount	
Calcium lactate	400 mg
Calcium glycerophosphate	400 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg
G3. 10 mg Tablet Formula.	
PPI: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other PPI in an equipotent amount	
Sodium bicarboante	750 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg

All of the tablets and powders of [illegible] Example may be swallowed whole, chewed or mixed with an aqueous medium prior to administration.

Example II

Standard Tablet of PPI and Buffering Agent.

Ten (10) tablets were prepared using a standard tablet press, each tablet comprising about 20 mg omeprazole and about 975 mg sodium bicarbonate uniformly dispersed throughout the tablet. To test the disintegration rate of the tablets, each was added to 60 ml of water. Using previously prepared liquid omeprazole/sodium bicarbonate solution as a visual comparator, it was observed that each tablet was completely dispersed in under three (3) minutes.

Another study using the tablets compounded according to this Example evaluated the bioactivity of the tablets in five (5) adult critical care patients. Each subject was administered one tablet via ng with a small amount of water, and the pH of ng aspirate was monitored using paper measure. The pH for each patient was evaluated for 6 hours and remained above 4, thus demonstrating the therapeutic benefit of the tablets in these patients.

Tablets were also prepared by boring out the center of sodium bicarbonate USP 975 mg tablets with a knife. Most of the removed sodium bicarbonate powder was then triturated with the contents of a 20 mg Prilosec® capsule and the resulting mixture was then packed into the hole in the tablet and sealed with glycerin.

Example III

PPI Central Core Tablet.

Tablets are prepared in a two-step process. First, about 20 mg of omeprazole is formed into a tablet as is known in the art to be used as a central core. Second, about 975 mg sodium bicarbonate USP is used to uniformly surround the central core to form an outer protective cover of sodium bicarbonate. The central core and outer cover are both prepared using standard binders and other excipients to create a finished, pharmaceutically acceptable tablet. The tablets may be swallowed whole with a glass of water.

Example IV

Effervescent Tablets and Granules.

The granules of one 20 mg Prilosec® capsule were emptied into a mortar and triturated with a pestle to a fine powder. The omeprazole powder was then geometrically diluted with about 958 mg sodium bicarbonate USP, about 832 mg citric acid USP and about 312 mg potassium carbonate USP to form a homogeneous mixture of effervescent omeprazole powder. This powder was then added to about 60 ml of water whereupon the powder reacted with the water to create effervescence. A bubbling solution resulted of omeprazole and principally the antacids sodium citrate and potassium citrate. The solution was then administered orally to one adult male subject and gastric pH was measured using pHydrion paper. The results were as follows:

Time Interval	pH Measured
Immediately prior to dose	2
1 hour post dose	7
2 hours post dose	6
4 hours post dose	6
6 hours post dose	5
8 hours post dose	4

One skilled in the art of pharmaceutical compounding will appreciate that bulk powders can be manufactured using the above ratios of ingredients, and that the powder can be pressed into tablets using standard binders and excipients. Such tablets are then mixed with water to activate the effervescent agents and create the desired solution. In addition, lansoprazole 30 mg (or an equipotent dose of other PPI) can be substituted for omeprazole.

The effervescent powder and tablets can alternatively be formulated by employing the above mixture but adding an additional 200 mg of sodium bicarbonate USP to create a resulting solution with a higher pH. Further, instead of the excess 200 mg of sodium bicarbonate, 100 mg of calcium glycerophosphate or 100 mg of calcium lactate can be employed. Combinations of the same can also added.

Example V

Parietal Cell Activator "Choco-Base™" Formulations and Efficacy.

Children are affected by gastro esophageal reflux disease (GERD) with atypical manifestations. Many of these atypical symptoms are difficult to control with traditional drugs such as H_2-antagonists, cisapride, or sucralfate. PPIs are more effective in controlling gastric pH and the symptoms of GERD than other agents. However, PPIs are not available in dosage forms that are easy to administer to young children. To address this problem, applicant employed omeprazole or lansoprazole in a buffered chocolate suspension (Choco-Base), in children with manifestations of GERD.

Applicant performed a retrospective evaluation of children with GERD referred to the University of Missouri-Columbia from 1995 to 1998 who received treatment with the experimental omeprazole or lansoprazole Choco-Base suspension formulated in accordance with Formulation 1 stated below. Data were included on all patients with follow up information sufficient to draw conclusions about pre/post treatment (usually >6 months). There were 25 patients who met the criteria for this evaluation. Age range was several weeks to greater than 5 years. Most patients had a history of numerous unsuccessful attempts at ameliorating the effects of GERD. Medication histories indicated many trials of various drugs.

The primary investigator reviewed all charts for uniformity of data collection. When insufficient data was available in the University charts, attempts were made to review charts in the local primary care physicians' offices for follow-up data. If information was still unavailable to review, attempts were made to contact family for follow-up. If data were still unavailable the patients were considered inevaluable.

Patient charts were reviewed in detail. Data noted were date of commencement of therapy, date of termination of therapy and any reason for termination other than response to treatment. Patient demographics were also recorded, as were any other medical illnesses. Medical illnesses were divided grossly into those that are associated with or exacerbate GERD and those that do not.

Patient charts were examined for evidence of response to therapy. As this was largely a referral population, and a

retrospective review, quantification of symptomatology based on scores, office visits and ED visits was difficult. Therefore, applicant examined charts for evidence of an overall change in patient symptoms. Any data to point towards improvement, decline or lack of change were examined and recorded.

Results

A total of 33 pediatric patients to date have been treated with the above-described suspension at the University of Missouri-Columbia. Of the 33 patients, 9 were excluded from the study, all based upon insufficient data about commencement, duration or outcome in treatment with PPI therapy. This left 24 patients with enough data to draw conclusions.

Of the 24 remaining patients, 18 were males and 6 females. Ages at implementation of PPI therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months [mean of 37 mo.]. Early on, reflux was usually documented by endoscopy and confirmed by pH probe. Eventually, pH probe was dropped and endoscopy was the sole method for documenting reflux, usually at the time of another surgery (most often T-tubes or adenoidectomy). Seven patients had pH probe confirmation of GERD, whereas 18 had endoscopic confirmation of reflux including all eight who had pH probing done (See FIGS. 5 and 6). Reflux was diagnosed on endoscopy most commonly by cobblestoning of the tracheal wall, with laryngeal and pharyngeal cobblestoning as findings in a few patients. Six patients had neither pH nor endoscopic documentation of GERD, but were tried on PPI therapy based on symptomatology alone.

Past medical history was identified in each chart. Ten patients had reflux-associated diagnoses. These were most commonly cerebral palsy, prematurity and Pierre Robin sequence. Other diagnoses were Charcot-Marie-Tooth disease, Velocardiofacial syndrome, Down syndrome and De George's syndrome. Non-reflux medical history was also identified and recorded separately (See Table 2 below).

Patients were, in general, referral patients from local family practice clinics, pediatricians, or other pediatric health care professionals. Most patients were referred to ENT for upper airway problems, sinusitis, or recurrent/chronic otitis media that had been refractory to medical therapy as reported by the primary care physician. Symptoms and signs most commonly found in these patients were recorded and tallied. All signs and symptoms were broken down into six major categories: (1) nasal; (2) otologic; (3) respiratory; (4) gastrointestinal; (5) sleep-related; and (6) other. The most common problems fell into one or all of the first 3 categories (See Table 1 below).

Most patients had been treated in the past with medical therapy in the form of antibiotics, steroids, asthma medications and other diagnosis-appropriate therapies. In addition, nine of the patients had been on reflux therapy in the past, most commonly in the form of conservative therapy such as head of bed elevation 30°, avoidance of evening snacks, avoidance of caffeinated beverages as well as cisapride and ranitidine (See FIG. 7).

The proton pump inhibitor suspension used in this group of patients was Choco-Base suspension of either lansoprazole or omeprazole. The dosing was very uniform, with patients receiving doses of either 10 or 20 mg of omeprazole and 23 mg of lansoprazole. Initially, in April of 1996 when therapy was first instituted 10 mg of omeprazole was used. There were 3 patients in this early phase who were treated initially with 10 mg po qd of omeprazole. All three subsequently were increased to either 20 mg po qd of omeprazole or 23 mg po qd of lansoprazole. All remaining patients were given either the 20 mg omeprazole or the 23 mg lansoprazole treatment qd, except in one case, where 30 mg of lansoprazole was used. Patients were instructed to take their doses once per day, preferably at night in most cases. Suspensions were all filled through the University of Missouri Pharmacy at Green Meadows. This allowed for tracking of usage through refill data.

Most patients responded favorably to and tolerated the once daily dosing of Choco-Base proton pump inhibitor suspension. Two patients had documented adverse effects associated with the use of the PPI suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment failure. The other patient had small amounts of bloody stools per mother. This patient never had his stool tested, as his bloody stool promptly resolved upon cessation of therapy, with no further sequellae. The other 23 patients had no documented adverse effects.

Patients were categorized based on review of clinic notes and chart review into general categories: (1) improved; (2) unchanged; (3) failed; and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of PPI therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical findings while on therapy, one complained of worsening symptoms while on therapy, one patient had therapy as prophylaxis for surgery, and two stopped therapy just after its commencement (see FIG. 8). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which PPI therapy was for purely prophylactic reasons, leaves (17/21) 81% of patients that responded to Choco-Base suspension. This means that 19% (4/21) of patients received no apparent benefit from PPI therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were mild bloody stool that completely resolved upon cessation of therapy.

Discussion

GERD in the pediatric population is relatively common, affecting almost 50% of newborns. Even though most infants outgrow physiologic reflux, pathologic reflux still affects approximately 5% of all children throughout childhood. Recently considerable data has pointed to reflux as an etiologic factor in extra-esophageal areas. GERD has been attributed to sinusitis, dental caries, otitis media, asthma, apnea, arousal, pneumonia, bronchitis, and cough, among others. Despite the common nature of reflux, there seems to have been little improvement in therapy for reflux, especially in the non-surgical arena.

The standard of therapy for the treatment of GERD in the pediatric population has become a progression from conservative therapy to a combination of a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, PPI therapy is effective in 90% of those treated for gastroesophageal reflux disease. As a medical alternative to the H-2 blockers, the proton pump inhibitors have not been studied extensively in the pediatric population. Part of the reason for this lack of data may be related to the absence of a suitable dosage formulation for this very young population, primarily under 2 years of age, that does not swallow capsules or tablets. It would be desirable to have a true liquid formulation (solution or suspension) with good palatability such as is used for oral antibiotics, decongestants, antihistamines, H-2 blockers, cisapride,

metoclopramide, etc. The use of lansoprazole granules (removed from the gelatin capule) and sprinkled on applesauce has been approved by the Food and Drug Administration as an alternative method of drug administration in adults but not in children. Published data are lacking on the efficacy of the lansoprazole sprinkle method in children. Omeprazole has been studied for bioequivalence as a sprinkle in adults and appears to produce comparable serum concentrations when compared to the standard capsule. Again no data are available on the omeprazole sprinkle in children. An additional disadvantage of omeprazole is its taste which is quinine-like. Even when suspended in juice, applesauce or the like, the bitter nature of the medicine is easily tasted even if one granule is chewed. For this reason applicant eventually progressed to use lansoprazole in Choco-Base. Pantoprazole and rabeprazole are available as enteric-coated tablets only. Currently, none of the proton pump inhibitors available in the United States are approved for pediatric use. There is some controversy as to what the appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective PPI dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity with the PPIs is not seen even at >50 mg/kg, there appears little risk associated with the higher dosages. Based on observations at the University of Missouri consistent with the findings of this review, applicant established a simple fixed dosage regimen of 10 ml Choco-Base suspension daily. This 10 ml dose provided 20 mg omeprazole or 23 mg lansoprazole.

In the ICU setting, the University of Missouri-Columbia has been using an unflavored PPI suspension given once daily per various tubes (nasogastric, g-tube, jejunal feeding tube, duo tube, etc.) for stress ulcer prophylaxis. It seemed only logical that if this therapy could be made into a palatable form, it would have many ideal drug characteristics for the pediatric population. First, it would be liquid, and therefore could be administered at earlier ages. Second, if made flavorful it could help to reduce noncompliance. Third, it could afford once daily dosing, also helping in reducing noncompliance. In the process, applicant discovered that the dosing could be standardized, which nearly eliminated dosing complexity.

Choco-Base is a product which protects drugs which are acid labile, such as proton pump inhibitors, from acid degradation. The first few pediatric patients with reflux prescribed Choco-Base were sicker patients. They had been on prior therapy and had been diagnosed both by pH probe and endoscopy. In the first few months, applicant treated patients with 10 mg of omeprazole qd (1 mg/kg) and found this to be somewhat ineffective, and quickly increased the dosing to 20 mg (2 mg/kg) of omeprazole. About halfway through the study, applicant began using lansoprazole 23 mg po qd. Applicant's standard therapy was then either 20 mg of omeprazole or 23 mg of lansoprazole once daily. The extra 3 mg of lansoprazole is related only to the fact that the final concentration was 2.25 mg/ml, and applicant desired to keep dosing simple, so he used a 10 ml suspension.

The patients that were treated represented a tertiary care center population, and they were inherently sicker and refractory to medical therapy in the past. The overall 72% success rate is slightly lower than the 90% success rates of PPIs in the adult population, but this can be attributed to the refractory nature of their illness, most having failed prior non-PPI treatment. The population in this study is not indicative of general practice populations.

Conclusion

PPI therapy is a beneficial therapeutic option in the treatment of reflux related symptoms in the pediatric population. Its once daily dosing and standard dosing scheme combined with a palatable formulation makes it an ideal pharmacologic agent.

TABLE 1

Symptoms	Patient Numbers
Nasal:	35
Sinusitis	7
Congestion	8
Nasal discharge	16
Other	4
Otologic:	26
Otitis Media	17
Otorrhea	9
Respiratory:	34
Cough	10
Wheeze	11
Respiratory Distress:	5
Pneumonia	2
Other	6
Gastrointestinal:	10
Abdominal Pain	1
Reflux/Vomiting	4
Other	4
Sleep Disturbances:	11
Other	2

TABLE 2

Past Medical History	Number of Patients
Reflux Associated:	12
Premature	5
Pierre-Robin	2
Cerebral Palsy	2
Down Syndrome	1
Charcot-Marie-Tooth	1
Velocardiofacial Syndrome	1
Other Medical History	12
Cleft Palate	3
Asthma	3
Autism	2
Seizure Disorder	1
Diabetes Mellitus	1
Subglottic Stenosis	1
Tracheostomy Dependent	1

FORMULATION I

PART A INGREDIENTS	AMOUNT (mg)
Omeprazole	200
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT (ml)**
Distilled Water	100

-continued

FORMULATION 1

COMPOUNDING INSTRUCTIONS

Add Part B to Part A to create a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.

FORMULATION 2

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5

PART B INGREDIENTS	AMOUNT
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg

COMPOUNDING INSTRUCTIONS

Mix the constituents of Part B together thoroughly and then add to Part A. This results in a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.

FORMULATION 3

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5

PART B INGREDIENTS	AMOUNT
Distilled Water	100 ml
Omeprazole	200 mg

COMPOUNDING INSTRUCTIONS

This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.

FORMULATION 4

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5

PART B INGREDIENTS	AMOUNT
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg

COMPOUNDING INSTRUCTIONS

This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.

In all four of the above formulations, lansoprazole or other PPI can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200 mg of omeprazole. Additionally, aspartame can be substituted for sucrose, and the following other ingredients can be employed as carriers, adjuvants and excipients: maltodextrin, vanilla, carrageenan, mono and diglycerides, and lactated monoglycerides. One skilled in the art will appreciate that not all of the ingredients are necessary to create a Choco-Base formulation that is safe and effective.

Omeprazole powder or enteric-coated granules can be used in each formulation. If the enteric-coated granules are used, the coating is either dissolved by the aqueous diluent or inactivated by trituration in the compounding process.

Applicant additionally analyzed the effects of a lansoprazole Choco-Base formulation on gastric pH using a pH meter (Fisher Scientific) in one adult patient versus lansoprazole alone. The patient was first given a 30 mg oral capsule of lansoprazole (Prevacid®), and the patient's gastric pH was measured at 0, 4, 8, 12, and 16 hours post dose. The results are illustrated in FIG. 4.

The ChocoBase product was compounded according to Formulation 1 above, except 300 mg of lansoprazole was used instead of omeprazole. A dose of 30 mg lansoprazole Choco-Base was orally administered at hour 18 post lansoprazole alone. Gastric pH was measured using a pH meter at hours 18, 19, 24, 28, 32, 36, 40, 48, 52, and 56 post lansoprazole alone dose.

FIG. 4 illustrates the lansoprazole/cocoa combination resulted in higher pH, at hours 19–56 than lansoprazole alone at hours 4–18. Therefore, the combination of the lansoprazole with chocolate enhanced the pharmacologic activity of the lansoprazole. The results establish that the sodium bicarbonate as well as chocolate flavoring and calcium were all able to stimulate the activation of the proton pumps, perhaps due to the release of gastrin. Proton pump inhibitors work by functionally inhibiting the proton pump and effectively block activated proton pumps (primarily those inserted into the secretory canalicular membrane). By further administering the proton pump inhibitor with one of these activators or enhancers, there is a synchronization of activation of the proton pump with the absorption and subsequent parietal cell concentrations of the

proton pump inhibitor. As illustrat[illegible]G. 4, this combination produced a much longer pharmacologic effect than when the proton pump inhibitor was administered alone.

Example VI

Combination Tablet Delivering Bolus And Time-Released Doses of PPI

Tablets were compounded using known methods by forming an inner core of 10 mg omeprazole powder mixed with 750 mg sodium bicarbonate, and an outer core of 10 mg omeprazole enteric-coated granules mixed with known binders and excipients. Upon ingestion of the whole tablet, the tablet dissolves and the inner core is dispersed in the stomach where it is absorbed for immediate therapeutic effect. The enteric-coated granules are later absorbed in the duodenum to provide symptomatic relief later in the dosing cycle. This tablet is particularly useful in patients who experience breakthrough gastritis between conventional doses, such as while sleeping or in the early morning hours.

Example VII

Therapeutic Application.

Patients were evaluable if they met the following criteria: had two or more risk factors for SRMD (mechanical ventilation, head injury, severe burn, sepsis, multiple trauma, adult respiratory distress syndrome, major surgery, acute renal failure, multiple operative procedures, coagulotherapy, significant hyportension, acid-base disorder, and hepatic failure), gastric pH of ≦4 prior to study entry, and no concomitant prophylaxis for SRMD.

The omeprazole solution was prepared by mixing 10 ml of 8.4% sodium bicarbonate with the contents of a 20 mg capsule of omeprazole (Merck & Co. Inc., West Point, Pa.) to yield a solution having a final omeprazole concentration of 2 mg/ml.

Nasogastric (ng) tubes were placed in the patients and an omeprazole dosage protocol of buffered 40 mg omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$ -8.4%) followed by 40 mg of the same buffered omeprazole solution in eight hours, then 20 mg of the same buffered omeprazole solution per day, for five days. After each buffered omeprazole solution administration, nasogastric suction was turned off for thirty minutes.

Eleven patients were evaluable. All patients were mechanically ventilated. Two hours after the initial 40 mg dose of buffered omeprazole solution, all patients had an increase in gastric pH to greater than eight as shown in FIG. 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four when administered 20 mg omeprazole solution. One patient required 40 mg omeprazole solution per day (closed head injury, five total risk factors for SRMD). Two patients were changed to omeprazole solution after having developed clinically significant upper gastrointestinal bleeding while receiving conventional intravenous H_2-antagonists. Bleeding subsided in both cases after twenty-four hours. Clinically significant upper gastrointestinal bleeding did not occur in the other nine patients. Overall mortality was 27%, mortality attributable to upper gastrointestinal bleeding was 0%. Pneumonia developed in one patient after initiating omeprazole therapy and was present upon the initiation of omeprazole therapy in another patient. The mean length of prophylaxis was five days.

A pharmacoeconomic analysis revealed a difference in the total cost of care for the prophylaxis of SRMD:

- ranitidine (Zantac®) continuous infusion intravenously (150 mg/24 hours)×five days $125.50;
- cimetidine (Tagamet®) [illegible]uous infusion intravenously (900 mg/24 hours)×five days $109.61;
- sucralfate one g slurry four times a day per (ng) tube×five days $73.00; and
- buffered omeprazole solution regimen per (ng) tube×five days $65.70.

This example illustrates the efficacy of the buffered omeprazole solution of the present invention based on the increase in gastric pH, safety and cost of the buffered omeprazole solution as a method for SRMD prophylaxis.

Example VIII

Effect on pH.

Experiments were carried out in order to determine the effect of the omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$-8.4%) administration on the accuracy of subsequent pH measurements through a nasogastric tube.

After preparing a total of 40 mg of buffered omeprazole solution, in the manner of Example VII, doses were administered into the stomach, usually through a nasogastric (ng) tube. Nasogastric tubes from nine different institutions were gathered for an evaluation. Artificial gastric fluid (gf) was prepared according to the USP. pH recordings were made in triplicate using a Microcomputer Portable pH meter model 6007 (Jenco Electronics Ltd., Taipei, Taiwan).

First, the terminal portion (tp) of the nasogastric tubes was placed into a glass beaker containing the gastric fluid. A 5 ml aliquot of gastric fluid was aspirated through each tube and the pH recorded; this was called the "pre-omeprazole solution/suspension measurement." Second, the terminal portion (tp) of each of the nasogastric tubes was removed from the beaker of gastric fluid and placed into an empty beaker. Twenty (20) mg of omeprazole solution was delivered through each of the nasogastric tubes and flushed with 10 ml of tap water. The terminal portion (tp) of each of the nasogastric tubes was placed back into the gastric fluid. After a one hour incubation, a 5 ml aliquot of gastric fluid was aspirated through each nasogastric tube and the pH recorded; this was called the "after first dose SOS [Simplified Omeprazole Solution] measurement." Third, after an additional hour had passed, the second step was repeated; this was called the "after second dose SOS [Simplified Omeprazole Solution] measurement." In addition to the pre-omeprazole measurement, the pH of the gastric fluid was checked in triplicate after the second and third steps. A change in the pH measurements of +/−0.3 units was considered significant. The Friedman test was used to compare the results. The Friedman test is a two way analysis of variance which is used when more than two related samples are of interest, as in repeated measurements.

The results of these experiments are outlined in Table 3.

TABLE 3

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
[1] gf Pre SOS	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[2] gf p 1st dose 1.3† check of gf pH	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[3] gf p 2nd Dose	1.3	1.3	1.4	1.4	1.4	1.3	1.4	1.3	1.3

TABLE 3-continued

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
1.3† check of gf pH									SOS pH = 9.0

Table 3 illustrates the results of the pH measurements that were taken during the course of the experiment. These results illustrate that there were no statistically significant latent effects of omeprazole solution administration (per nasogastric tube) on the accuracy of subsequent pH measurements obtained through the same nasogastric tube.

Example IX

Efficacy of Buffered Omeprazole Solution in Ventilated Patients.

Experiments were performed in order to determine the efficacy, safety, and cost of buffered omeprazole solution in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Patients

Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage.

Interventions

Patients received 20 ml omeprazole solution (prepared as per Example VII and containing 40 mg of omeprazole) initially, followed by a second 20 ml dose six to eight hours later, then 10 ml (20 mg) daily. Omeprazole solution according to the present invention was administered through a nasogastric tube, followed by 5–10 ml of tap water. The nasogastric tube was clamped for one to two hours after each administration.

Measurements and Main Results

The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage and was associated with a five percent decrease in hematocrit. Secondary efficacy measures were gastric pH measured four hours after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the incidence of adverse events and the incidence of pneumonia. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric pH was 7.1 (mean), the mean gastric pH after starting omeprazole was 6.8 (mean) and the lowest pH after starting omeprazole was 5.6 (mean). The incidence of pneumonia was twelve percent. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions

Omeprazole solution prevented clinically significant upper gastrointestinal bleeding and maintained gastric pH above 5.5 in mechanically ventilated critical care patients without producing toxicity.

Materials and Methods

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population

All adult (>18 years old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated intensive care unit stay of at least forty-eight hours were considered for inclusion in the study. To be included patients also had to have a gastric pH of <4, had to be mechanically ventilated and have one of the following additional risk factors for a minimum of twenty-four hours after initiation of omeprazole suspension: head injury with altered level of consciousness, extensive burns (>20% Body Surface Area), acute renal failure, acid-base disorder, multiple trauma, coagulopathy, multiple operative procedures, coma, hypotension for longer than one hour or sepsis (see Table 4). Sepsis was defined as the presence of invasive pathogenic organisms or their toxins in blood or tissues resulting in a systematic response that included two or more of the following: temperature greater than 38° C. or less than 36° C., heart rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute (or $_pO_2$ less than 75 mm Hg), and white blood cell count greater than 12,000 or less than 4,000 cells/mm^3 or more than 10 percent bands (Bone, *Let's Agree on Terminology: Definitions of Sepsis*, Crit. Care Med., 19:27 (1991)). Patients in whom H_2-antagonist therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count less than 30,000 cells/mm^3); were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH above four for forty-eight hours after ICU admission (without prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having non-stress-related mucosal bleeding. The reason for this exclusion is the confounding effect of non-stress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration

Omeprazole solution was prepared immediately before administration by the patient's nurse using the following instructions: empty the contents of one or two 20 mg omeprazole capsule(s) into an empty 10 ml syringe (with 20 gauge needle in place) from which the plunger has been removed. (Omeprazole delayed-release capsules, Merck & Co., Inc., West Point, Pa.); replace the plunger and uncap the needle; withdraw 10 ml of 8.4% sodium bicarbonate solution or 20 ml if 40 mg given (Abbott Laboratories, North Chicago, Ill.), to create a concentration of 2 mg omeprazole per ml of 8.4% sodium bicarbonate; and allow the enteric coated pellets of omeprazole to completely breakdown, ~30 minutes (agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before administration. The solution was not administered with acidic substances. A high-pressure liquid chromatography study was performed that demonstrated that this preparation of simplified omeprazole suspension maintains >90% potency for seven days at room temperature. This preparation remained free of bacterial and fungal contamination for thirty days when stored at room temperature (See Table 7).

The initial dose of omeprazole solution was 40 mg, followed by a second 40 mg dose six to eight hours later, then a 20 mg daily dose administered at 8:00 AM. Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5–10 ml of tap water and clamped for at least one hour. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube was removed and the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures

The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-minute lavage or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, Calif.) positive coffee ground material for four consecutive hours that did not clear with lavage (at least 100 ml) and produced a 5% decrease in hematocrit.

Secondary Outcome Measures

The secondary efficacy measures were gastric pH measured four hours after omeprazole was administered, mean gastric pH after starting omeprazole and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, N.Y.) was used to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of one pH unit. Gastric pH was measured before the initiation of omeprazole solution therapy, immediately before each dose, and every four hours between doses.

Other secondary outcome measures were incidence of adverse events (including drug interactions) and pneumonia. Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Prevention and Control definition of nosocomial pneumonia (Garner et al., 1988). According to these criteria, a patient who has pneumonia is one who has rales or dullness to percussion on physical examination of the chest or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and has at least two of the following present: new purulent sputum or changes in character of the sputum, an organism isolated from blood culture, fever or leukocytosis, or evidence of infection from a protective specimen brush or bronchoalveolar lavage. Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia incidence figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present prior to the start of omeprazole suspension.

Cost of Care Analysis

A pharmacoeconomic evaluation of stress ulcer prophylaxis using omeprazole solution was performed. The evaluation included total drug cost (acquisition and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental confusion), costs associated with clinically significant upper gastrointestinal bleeding. Total drug cost was calculated by adding the average institutional costs of omeprazole 20 mg capsules, 50 ml sodium bicarbonate vials, and 10 ml syringes with needle; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

Statistical Analysis

The paired t-test (two-tailed) was used to compare gastric pH before and after omeprazole solution administration and to compare gastric pH before omeprazole solution administration with the mean and lowest gastric pH value measured after beginning omeprazole.

Results:

Seventy-seven patients met the inclusion and exclusion criteria and received omeprazole solution (See FIG. 2). Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down prior to the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above six as soon as the patient was given a dose of omeprazole solution (in which the enteric coated pellets of omeprazole had been allowed to completely breakdown).

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained above four in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared failures, their pH values were no longer followed.

The ages of the remaining seventy-five patients ranged from eighteen to eighty-seven years; forty-two patients were male and thirty-three were female. All patients were mechanically ventilated during the study. Table 4 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was two to ten, with a mean of 3 (±1) (standard deviation). Five patients enrolled in the study had developed clinically significant bleeding while receiving continuous infusions of ranitidine (150 mg/24 hr) or cimetidine (900 mg/24 hr). In all five cases, the bleeding subsided and the gastric pH rose to above five within thirty-six hours after initiating omeprazole therapy. Three patients were enrolled after having developed two consecutive gastric pH values below three while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH rose to above five within four hours after omeprazole therapy was initi-

ated. Four other patients were enrolled in this study after experiencing confusion (n=2) or thrombocytopenia (n=2) during H_2-antigens therapy. Within thirty-six hours of switching therapy, these adverse events resolved.

Stress-related Mucosal Bleeding and Mortality

None of the sixty-five patients who received buffered omeprazole solution as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only (Gastroccult-positive) within eighteen hours of starting omeprazole solution; bleeding stopped in all patients within thirty-six hours. The overall mortality rate in this group of critically ill patients was eleven percent. No death was attributable to upper gastrointestinal bleeding or the use of omeprazole solution.

Gastric pH

The mean (± standard deviation) pre-omeprazole gastric pH was 3.5±1.9. Within four hours of omeprazole administration, the gastric pH rose to 7.1±1.1 (See FIG. 3); this difference was significant ($p<0.001$). The differences between pre-omeprazole gastric pH and the mean and lowest gastric pH measurements during omeprazole administration (6.8±0.6 and 5.6±1.3, respectively) were also statistically significant ($p<0.001$).

Safety

Omeprazole solution was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have been drug-related thrombocytopenia. However, the platelet count continued to fall after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus was unable to continue on omeprazole. No clinically significant drug interactions with omeprazole were noted during the study period. As stated above, metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in omeprazole solution was small (~12 mEq/10 ml) and no electrolyte abnormalities were found.

Pneumonia

Pneumonia developed in nine (12%) patients receiving omeprazole solution. Pneumonia was present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic evaluation

The average length of treatment was nine days. The cost of care data are listed in Tables 5 and 6. The costs of drug acquisition, preparation, and delivery for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 5. There were no costs to add from toxicity associated with omeprazole solution. Since two of seventy-five patients required 40 mg of omeprazole solution daily to adequately control gastric pH, the acquisition/preparation cost should reflect this. The additional 20 mg of omeprazole with vehicle adds seven cents per day to the cost of care. Therefore, the daily cost of care for omeprazole solution in the prophylaxis of stress-related mucosal bleeding was $12.60 (See Table 6).

Omeprazole solution is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has been challenged recently. All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage—mechanical ventilation. Previous trials and data from a recently published study show that stress ulcer prophylaxis is of proven benefit in patients at risk and, therefore, it was thought to be unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during omeprazole solution therapy. Gastric pH was maintained above 4 on omeprazole 20 mg/day in seventy-three of seventy-five patients. No adverse events or drug interaction associated with omeprazole were encountered.

TABLE 4

Mech Vent	Major Surgery	Multi-trauma	Head Injury	Hypo-tension	Renal Failure	Sepsis	Multiple Operation	Acid/Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2

Risk factors present in patients in this study (n = 75)

TABLE 5

		Per day
RANITIDINE (day 1–9)		
Rantidine	150 mg/24 hr	6.15
Ancillary Product (1)	Piggyback (60%)	0.75
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	0.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs × 50%)	14.50
TOTAL for 9 days		304.20
RANITIDINE Cost per day		33.80
CIMETIDINE (day 1–9)		
Cimetidine	900 mg/24 hr	3.96
Ancillary Product (1)	Piggyback	1.25
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	0.40
Sterile Prep required	yes	8.00
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs × 50%)	14.50
TOTAL for 9 days		288.99
CIMETIDINE Cost per day		32.11
SUCRALFATE (day 1–9)		
Sucralfate	1 g × 4	2.40
Ancillary Product (1)	syringe	0.20
Sterile Prep required	no	
RN. time ($24/hr)	30 minutes/day (includes pH monitoring)	12.00
TOTAL for 9 days		131.40
SUCRALFATE Cost per day		14.60

Note:
Does not include the cost of failure and/or adverse effect.
Acquisition, preparation and delivery costs of traditional agents.

TABLE 6

The average length of treatment was 9 days.
Cost of care was calculated from these date

		Per Day	Total
OMEPRAZOLE (day 1)			
Product acquisition cost	40 mg load x 2 (5.66/dose)	11.32	11.32
Ancillary product	materials for solution preparation	0.41	0.41
Ancillary product	syringe w/needle	0.20	0.40
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
OMEPRAZOLE (days 2-9)			
Product acqusition cost	20 mg per day	2.80	22.65
Ancillary product	materials for solution preparation	0.41	0.82
Ancillary product	syringe w/needle	0.20	1.60
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	18 minutes/day (includes pH monitoring)	8.40	57.60
2/75 patient require 40 mg simplified omeparzole solution per day (days 2-9)			0.63
No additional cost for adverse effects or for failure			
TOTAL			113.43
Simplified Omerprazole Solution cost per day			12.60

Pharmacoeconomic evaluation of omeprazole cost of care

TABLE 7

Time	Control	1 hour	24 hour	2 day	7 day	14 day
Conc (mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

Stability of Simplified Omeprazole Solution at room temperature (25° C.)
Values are the mean of three samples

Example X

Bacteriostatic and Fungistatic Effects of Omeprazole Solution

The antimicrobial or bacteriostatic effects of the omeprazole solution were analyzed by applicant. An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made according to the present invention was stored at room temperature for four weeks and then was analyzed for fungal and bacterial growth. Following four weeks of storage at room temperature, no bacterial or fungal growth was detected.

An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made in accordance with the present invention was stored at room temperature for twelve weeks and then was analyzed for fungal and bacterial growth. After twelve weeks of incubation at room temperature, no fungal or bacterial growth was detected.

The results of these experiments illustrate the bacteriostatic and fungistatic characteristics of the omeprazole solution of the present invention.

Example XI

A. Bioequivalency Study.

Healthy male and female study participants over the age of 18 will be randomized to receive omeprazole in the following forms:

(A) 20 mg of a liquid formulation of approximately 20 mg omeprazole in 4.8 mEq sodium bicarbonate qs to 10 ml with water;

(B) 20 mg of a liquid formulation of approximately 2 mg omeprazole per 1 ml of 8.4% sodium bicarbonate.

(C) Prilosec® (omeprazole) 20 mg capsule;

(D) Capsule prepared by inserting non-enteric coated omeprazole 20 mg into a #4 empty gelatin capsule (Lilly) uniformly dispersed in 240 mg of sodium bicarbonate powder USP to form an inner capsule. The inner capsule is then inserted into a #00 empty gelatin capsule (Lilly) together with a homogeneous mixture of 600 mg sodium bicarbonate USP and 110 mg pregelatinized starch NF.

After appropriate screening and consent, healthy volunteers will be randomized to receive one of the following four regimens as randomly assigned by Latin Square. Each subject will be crossed to each regimen according to the randomization sequence until all subjects have received all four regimens (with one week separating each regimen).

Regimen A (20 mg omeprazole in 4.8 mEq sodium bicarbonate in 10 ml volume); Regimen B (20 mg omeprazole in 10 ml 8.4% sodium bicarbonate in 10 ml volume); Regimen C (an intact 20 mg omeprazole capsule); Regimen D (Capsule in capsule formulation, see above). For each dose/week, subjects will have an i.v. saline lock placed for blood sampling. For each regimen, blood samples will be taken over 24 hours a total of 16 times (with the last two specimens obtained 12 hours and 24 hours after drug administration).

B. Patient Eligibility

Four healthy females and four healthy males will be consented for the study.

C. Inclusion Criteria

Signed informed consent.

D. Exclusion Criteria

1. Currently taking H_2-receptor antagonist, antacid, or sucralfate.
2. Recent (within 7 days) therapy with lansoprazole, omeprazole, or other proton pump inhibitor.
3. Recent (within 7 days) therapy with warfarin.
4. History of variceal bleeding.
5. History of peptic ulcer disease or currently active G.I. bleed.
6. History of vagotomy or pyloroplasty.

7. Patient has received an investigational drug within 30 days.
8. Treatment with ketoconazole or itraconazole.
9. Patient has an allergy to omeprazole.

E. Pharmocokinetic Evaluation and Statistical Analysis

Blood samples will be centrifuged within 2 hours of collection and the plasma will then separated and frozen at −10° C. (or lower) until assayed. Pharmacokinetic variables will include: time to peak concentration, mean peak concentration, AUC (0-t) and (0-infinity). Analysis of variance will be used to detect statistical difference. Bioavailability will be assessed by the 90% confidence interval of the two one-sided tests on the natural logarithm of AUC.

F. HPLC Analysis

Omeprazole and internal standard (H168/24) will be used. Omeprazole and internal standard will be measured by modification of the procedure described by Amantea and Narang. (Amantea M A, Narang P K. *Improved Procedure for Quantification of Omeprazole and Metabolites Using Reversed-Phased High Performance Liquid Chromotography*. J. Chromatography 426; 216–222 (1988)). Briefly, 20 ul of omeprazole 2 mg/ml $NaHCO_3$ or Choco-Base omeprazole suspension and 100 ul of the internal standard are vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml of dichloroethane, 5 ml of hexane, and 980 ul of sterile water. After the sample is centrifuged, the organic layer is extracted and dried over a nitrogen stream. Each pellet is reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul is injected onto a C_{18} 5 U column equilibrated with the same mobile phase at 1.1 ml/min. Under these conditions, omeprazole is eluted at approximately 5 minutes, and the internal standard at approximately 7.5 minutes. The standard curve is linear over the concentration range 0–3 mg/ml (in previous work with SOS), and the between-day coefficient of variation has been <8% at all concentrations. The typical mean R^2 for the standard curve has been 0.98 in prior work with SOS (omeprazole 2 mg/ml $NaHCO_3$ 8.4%).

Applicant expects that the above experiments will demonstrate there is more rapid absorption of formulations (a), (b) and (d) as compared to the enteric coated granules of formulation (c). Additionally, applicant expects that although there will be a difference in the rates of absorption among forms (a) through (d), the extent of absorption (as measured by the area under the curve (AUC)) should be similar among the formulations (a) through (d).

Example XII

Intraveneous PPI in Combination With Oral Parietal Cell Activator

Sixteen (16) normal, healthy male and female study subjects over the age of 18 will be randomized to receive pantoprazole as follows:

(a) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of sodium bicarbonate 8.4%; and
(b) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of water.

The subjects will receive a single dose of (a) or (b) above, and will be crossed-over to (a) and (b) in random fashion. Serum concentrations of pantoprazole versus time after administration data will be collected, as well as gastric pH control as measured with an indwelling pH probe.

Further, similar studies are contemplated wherein chocolate or other parietal cell activator is substituted for the parietal cell activator sodium bicarbonate, and other PPIs are substituted for pantoprazole. The parietal cell activator can be administered either within about 5 minutes before, during or within about 5 minutes after the IV dose of PPI.

Applicant expects that these studies will demonstrate that significantly less IV PPI is required to achieve therapeutic effect when it is given in combination with an oral parietal cell activator.

Additionally, administration kits of IV PPI and oral parietal cell activator can be packaged in many various forms for ease of administration and to optimize packing and shipping the product. Such kits can be in unit dose or multiple dose form.

Example XIII

Six (6) Month Stability of Omeprazole Suspension.

A suspension was prepared by mixing 8.4% sodium bicarbonate with omeprazole to produce a final concentration of 2 mg/ml to determine the stability of omeprazole solution after 6 months. The resultant preparation was stored in clear glass at room temperature, refrigerated and frozen. Samples were drawn after thorough agitation from the stored preparations at the prescribed times. The samples were then stored at 70° C. Frozen samples remained frozen until they were analyzed. When the collection process was completed, the samples were shipped to a laboratory overnight on dry ice for analysis. Samples were agitated for 30 seconds and sample aliquots were analyzed by HPLC in triplicate according to well known methods. Omeprazole and the internal standard were measured by a modification of the procedure described by Amantea and Narang. (Amantea M A, Narang P K, *Improved Procedure For Quantitation Of Omeprazole And Metabolites Using Reverse-Phased High-Performance Liquid Chromatography*, J. Chromatography, 426: 216–222 (1988)). Twenty (20) ul of the omeprazole 2 mg/ml $NaHCO_3$ solution and 100 ul of the internal standard solution were vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml dichloroethane, 5 ml hexane, and 980 ul of sterile water. The sample was centrifuged and the organic layer was extracted and dried over a nitrogen stream. Each pellet was reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul were injected onto a C185 u column equilibrated with the same mobile phase at 1.1 ml/min. Omeprazole was eluted at ~5 min, and the internal standard at ~7.5 min. The standard curve was linear over the concentrated range 0–3 mg/ml, and between-day coefficient of variation was <8% at all concentrations. Mean R^2 for the standard curve was 0.980.

The 6 month sample showed stability at greater than 90% of the original concentration of 2 mg/ml. (i.e., 1.88 mg/ml, 1.94 mg/ml, 1.92 mg/ml).

VI. PPI Compositions and Method for Optimizing the Buffer to be Administered in Combination With a PPI

A. Introduction

The compositions of the present invention are designed to produce rapid release of active drug to the site of delivery (typically the stomach) without the necessity of enteric coatings or delayed released dosage forms, while preventing acid degradation of the drug. Acid labile PPIs, for example, can be formulated or coadministered with one or more buffers sufficient to protect the PPI in any environment, with the ultimate goal being to deliver a PPI to the stomach (or other environment) either via a liquid, a powder or solid dosage form that produces an immediate release of active drug to the site of delivery such that the PPI is quickly

available for absorption. Accordingly, Applicant has found that certain amounts of buffers coadministered or mixed with certain PPIs prevent acid degradation of the PPI when the buffers produce a pH in the stomach or other site of environment that is equal to the pKa of the PPI plus an amount sufficient to protect the PPI from acids and provide undegraded and bioactive PPI to the blood upon administration (e.g., a final pH of pKa of PPI+0.7 log value will reduce the degradation to about 10%). Such buffers should interact with hydrogen ion at rates that exceed the interaction of hydrogen ion with the PPI. Thus, the solubilities of the buffers and PPIs are important considerations because solubility is a key determinant of the rate of interaction of H+ ion with another compound.

Typically, a PPI formulation of the present invention comprises two primary components: a PPI and an Essential Buffer. An Essential Buffer may include a buffer or combination of buffers that interact with HCl (or other acids in the environment of interest) faster than the PPI interacts with the same acids. When placed in a liquid phase (usually in water), the Essential Buffer produces and maintains a pH of at least the pKa of the PPI. In one embodiment, by raising the pH of the environment to the same of the pKa of the PPI plus about 0.7 log value (or greater), the expected degradation (ionization) can be reduced from about 50% to about 10%. As used herein, the "Essential pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the PPI. The buffering agent(s) employed may raise the pH of the environment to the Essential pH such that 30%, 40% or 50% of the PPI is undegraded, or be present in an amount sufficient to substantially protect (i.e., greater than 50% stability) the PPI.

In another embodiment, the Essential pH is the pKa of the PPI. In a further embodiment, the Essential pH is the sum of the pKa of the PPI plus log 0.7. A log value of about 0.7 is added to the pKa, which represents a decrease of about 5.01187% in stability of the PPI from the pKa plus 1 log value, thus resulting in a stability of approximately 90%, a value widely accepted as desirable in pharmaceutical products. In some cases it may be permissible to accept a value of less than log 0.7.

One aspect of the invention provides that there is also sufficient buffer available to provide the neutralization capacity (Essential Buffer Capacity ("EBC")) to maintain the elevated pH of the environment (usually gastric) throughout the dwell time that the PPI is passed from the environment and into the blood.

B. Essential Buffers

Essential Buffers can be divided into two groups: Primary Essential Buffers and Secondary Essential Buffers. Every formulation is combined with, either directly or indirectly, at least one Primary Essential Buffer. The Primary Essential Buffers, when used alone or in combination, provide buffering activity below the value that leads to tissue irritation or damage and above a lower limit for the Essential pH of the PPI. Secondary Essential Buffers are not required in every formulation but can be combined with Primary Essential Buffers to produce a higher pH and added neutralization capacity for the formulation.

Determining the type and dose of buffer to protect acid labile substituted benzimidazole PPIs (and other drugs) is useful for efficacious PPI delivery to and action upon parietal cell proton pumps, particularly when the PPI is administered as an immediate release product designed to disintegrate in the stomach rather than a traditional delayed-release product designed to disintegrate beyond the stomach in higher pH environments such as the duodenum. The present compositions and methods employ determinations of the nature of the buffer(s) to be used, as well as calculations to determine Essential pH, buffering capacity, and volume measurements for individual PPI doses based on their respective solubilities and pKa's. Such inventive methods are applicable for determining the type and amount of buffer(s) necessary to protect the PPI in an array of environments (e.g., mouth, esophagus, stomach, duodenum, jejunum, rectal vault, nasogastric tube, or a powder, tablet, capsule, liquid, etc. in storage before administration). Dosage forms in storage may be exposed to various environments, but a typical set of storage conditions includes storage at room temperature (65–80° F.), and minimal or no exposure to heat, cold, light or humidity as is known in the art.

The present method includes all substituted benzimidazole PPIs, their salts, esters, amides, enantiomers, racemates, prodrugs, derivatives and the like, and is not limited to those PPIs used to exemplify the following calculations.

The Essential Buffering Capacity ("EBC") is the capacity of a PPI/buffer formulation to resist degradation from its environment. The buffering capacity of a PPI/buffer formulation is primarily derived from components of the formulation that possess the ability to combine with acids (H+ ions) from the environment. The EBC contributes to both acid neutralization (antacid effect) and to maintaining an environmental pH>pKa+0.7 to protect PPIs from acid degradation throughout the dwell time. The Primary Essential Buffer is designed to maintain the pH of stomach contents (or other environment) at a somewhat constant level within a desired range for a period of time so that the PPI can be absorbed from the gastric or other environment. Accordingly, the Essential Buffer is generally more rapid in its complexation with HCl (or other acid) than the PPI administered so that the Essential Buffer is capable of protecting the PPI.

Any weak base, strong base, or combination thereof may be a suitable Essential Buffer. Essential Buffers include, but are not limited to, electrolytes containing the cations sodium, potassium, calcium, magnesium or bismuth. In addition, amino acids, proteins or protein hydrolysates can serve as Essential Buffers owing to their ability to rapidly neutralize acid. When PPIs are mixed with the Essential Buffer, the PPIs may be in the free base form, such as omeprazole or lansoprazole; in the sodium salt form, such as esomeprazole sodium, omeprazole sodium, rabeprazole sodium, pantoprazole sodium, etc.; or in a magnesium salt form such as esomeprazole magnesium or omeprazole magnesium or calcium salt forms; or other salt forms. Essential Buffers provide the Essential Buffering Capacity either alone or in combination with Secondary Essential Buffers.

Tribasic sodium phosphate and sodium carbonate are examples of Secondary Essential Buffers for adjusting the pH of any Primary Essential Buffer. Secondary Essential Buffers may assist the Primary Essential Buffer in producing the desirable pH_E over the dwell time. Secondary Essential Buffers neutralize HCl (or other acids in the environment) similarly to the Primary Essential Buffers; however, they produce pH values too high to be used alone, as they would lead to gastrointestinal mucosal irritation. They are used to increase the pH and provide additional buffering capacity in combination with a Primary Essential Buffer.

Secondary Essential Buffers do not play an important role in protecting the PPI from early acid-induced degradation. Because they do not work as rapidly, they do not play a major role in PPI protection through the dwell time. Other buffers ("Non-Essential Buffers") can be added to the Pri-

mary and/or Secondary Essential Buffers to provide a latent antacid effect that extends beyond the antacid effect of Essential Buffers.

Many additional buffers can be used, alone or in combination, to achieve an effective buffering capacity for PPIs or acid labile drugs. A desirable characteristic of buffers includes rapid neutralization of acid environments to greater than pKa+0.7 for the drug being considered.

Non-limiting examples of Primary and Secondary Essential Buffers are set forth in Tables 8 and 9 below.

TABLE 8

Examples of Primary Essential Buffers

Essential Buffer	Solubility‡	pH§	MW
Sodium bicarbonate	9.96 g/100 mL	8–8.4	84
Sodium sesquicarbonate	6.3 g/100 mL	9.9–10	174
Dibasic sodium phosphate	10 g/100 mL	8.6–9.3	142
Sodium tripolyphosphate	6 gm/100 mL	9.7–10	368
Tetrasodium pyrophosphate	5 g/100 mL	9.8–10.3	266
Sodium citrate	72 g/100 mL	5	294
Calcium citrate	10 mg/100 mL	6.8	498
Calcium carbonate	1.5 mg/100 mL	6.1–7.1	100
Magnesium oxide	0.62 mg/100 mL	9.5–10.5	40
Sodium gluconate	60 g/100 mL	6–8	218
Sodium lactate	40 g/100 mL	7	112
Sodium acetate	119 g/100 mL	8.9	82
Dipotassium phosphate	150 g/100 mL	9.3	174
Tetrapotassium pyrophosphate	185 g/100 mL	10.4	330
Potassium bicarbonate	36 g/100 mL	8.2	100
Calcium lactate	6 g/100 mL	7	218
Calcium glycerophosphate	6 g/100 mL	7	210
Calcium gluconate	3 g/100 mL	7.4	430
Magnesium lactate	10 g/100 mL	5.5–7.5	269
Magnesium gluconate	16 g/100 mL	7.3	414

‡solubility is altered by temperature
§pH is altered by concentration and temperature
Note: hydrated and anhydrous forms are acceptable provided they meet the criteria of a Primary Essential Buffer.

TABLE 9

Examples of Secondary Essential Buffers
These buffers are too caustic to be used alone but are suitable for addition in low quantities to the Primary Essential Buffers from Table 8.

Essential Buffer	Solubility‡	pH§	MW
Sodium carbonate	45.5 g/100 mL	10.6–11.4	106
Potassium carbonate		11.5	138
Sodium phosphate (tribasic)	8 g/100 mL	10.7–12.1	163
Calcium hydroxide	185 mg/100 mL	12	74
Sodium hydroxide		11.4–13.2	40

‡solubility is altered by temperature
§pH is altered by concentration and temperature
Note: hydrated and anhydrous forms are acceptable provided they meet the criteria of a Secondary Essential Buffer.

Amino acids can also be employed as Primary or Secondary Essential Buffers, the doses of which may be calculated according to the following information.

TABLE 10

One Letter Symbol	Three Letter Symbol	Amino Acid	MW	pH	Solubility (g/100 g H2O at 25° C.
A	Ala	Alanine	89	6	16.65
C	Cys	Cysteine	121	5.02	Very
D	Asp	Aspartic Acid	133	2.77	0.778

TABLE 10-continued

One Letter Symbol	Three Letter Symbol	Amino Acid	MW	pH	Solubility (g/100 g H2O at 25° C.
E	Glu	Glutamic Acid	147	3.22	0.864
F	Phe	Phenylalanine	165	5.48	2.965
G	Gly	Glycine	75	5.97	24.99
H	His	Histidine	155	7.47	4.19
I	Ile	Isoleucine	133	5.94	4.117
K	Lys	Lysine	146	9.59	Very
L	Leu	Leucine	131	5.98	2.426
M	Met	Methionine	149	5.74	3.381
N	Asn	Asparagine	132	5.41	3.53
P	Pro	Proline	115	6.30	162.3
Q	Gln	Glutamine	146	5.65	2.5
R	Arg	Arginine	174	11.15	15
S	Ser	Serine	105	5.68	5.023
T	Thr	Threonine	119	5.64	Very
V	Val	Valine	117	5.96	8.85
W	Trp	Tryptophan	204	5.89	1.136
Y	Tyr	Tyrosine	181	5.66	0.0453

References:
IUPAC-IUB Commission on Biochemical Nomenclature (CBN), Rules for Naming Synthetic Modifications of Natural Peptides, (1966); Arch. Biochem. Biophys. 121: 6–8 (1967); Biochem. J. 104: 17–19 (1967), corrected 135: 9 (1973); Biochemistry 6: 362–364 (1967); Biochim. Biophys. Acta 133: 1–5 (1967); Bull. Soc. Chim. Biol. 49: 325–330 (1967) (in French); Eur. J. Biochem. 1: 379–381 (1967), corrected 45: 3 (1974); Hoppe-Seyler's,Z., Physiol. Chem. 348: 262–265 (1967) (in German); J. Biol. Chem. 242 555–557 (1967); Mol. Biol. 2: 466–469 (1968) (in Russian); Pure Appl. Chem. 31: 647–653 (1972); *IUPAC Commission on Nomenclature of Organic Chemistry (CNOC), Nomenclature of Organic Chemistry*, Stereochem. Rec. E: (1974), Pure Appl. Chem. 45: 11–30 (1976). See also *Biochemical Nomenclature and Related Documents*, Portland Press. 2: 1–18 (1992).

C. The Essential pH (pH_E)

Substituted benzimidazole PPIs are labile under acidic conditions. Orally administered PPIs must be protected from the strongly acidic conditions of the stomach, whether acidic from gastric acids or acids introduced through tube feeds or other sources. In general, the higher the pH of the gastric environment, the greater the stability of the PPI, and thus the more time it has to undergo absorption into the blood and reach and act upon the proton pumps of the gastric parietal cells.

As mentioned, the "Essential pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the PPI during the dwell time in the environment. It is generally expressed herein as pH range. Such pH is the pH of the environment in which the PPI/buffer formulation resides. For example, the environment may be a storage container or the stomach. The environment presents a set of conditions to the PPI/buffer, such as temperature, pH, and the presence or absence of water. The dwell time is the time that the PPI dwells in a specific environment, i.e., the GI tract prior to its passage into a different environment, i.e. the bloodstream. The shelf-life is another example of a dwell time, in which case, the specific environment may be a container of dry, powdered formulation. As used herein, "Resultant pH" is the pH that is the result of adding a PPI/buffer formulation to an environment of interest. "Formulation pH" is the pH of the PPI/buffer formulation when it is in liquid form.

A PPI dose within its calculated pH_E range is designed to ensure sufficient PPI protection from acid degradation such

that delivery to and action upon proton pumps occur. In one desirable embodiment, the pH_E is the sum of the pKa of a given PPI plus about 0.7. The pKa is defined as the pH at which 50% of a chemical is in the ionized form. When the pH of the environment equals the pKa of the PPI, then 50% ionization (degradation) of the PPI occurs. However, by adding the factor of 0.7, this ionization is reduced to 90%.

The Stability Range Factor ("SRF") is the range of pH elevation in which the lower limit is the sum of the pKa of a given PPI+0.7 log, and the upper limit is the pH at which elimination of acid degradation occurs without producing tissue irritation from extreme alkalinity. SRF is calculated based on the desirable shelf-life (or a dwell time), the environmental pH and the amount of acid expected to be encountered, along with a knowledge of the time of exposure expected after the drug is administered and before the drug reaches the blood (i.e., the dwell time).

The upper limit of the SRF is a function of the tolerability of the gastrointestinal mucosa to alkaline substances, which is determined by the Formulation pH and the concentration of alkaline material presented. For practical purposes, pH=10.9 delineates an upper limit of the SRF. It is acknowledged that the amount of buffer is an important aspect of the tissue destructive potential of an alkaline substance. Therefore, the SRF for any given PPI begins at the sum of the pKa of the PPI+0.7, and extends upwards to a pH of about 10.9.

The Essential pH used with the SRF establishes a desirable range for the stability to the actions of H+ ion (or other acidic component) on the PPI/buffer formulation. Sufficient buffering capacity maintains an Essential pH as described below as "Essential Buffering Capacity."

Examples of pH_E calculations with SRF for specific PPIs are as follows:

pH_E of PPI=pKa of PPI+0.7.

SRF=the range: pH_E to 10.9.

SRF for omeprazole=(pKa omeprazole+0.7) to 10.9=(3.9+0.7)=4.6 to 10.9.

SRF for lansoprazole=(pKa lansoprazole+0.7) to 10.9=(4.1+0.7)=4.8 to 10.9.

SRF for rabeprazole=(pKa rabeprazole+0.7) to 10.9=(4.9+0.7)=5.6 to 10.9.

SRF for pantoprazole=(pKa pantoprazole+0.7) to 10.9=(3+0.7)=3.7 to 10.9.

In most instances, the lower end of each of the above ranges is increased by one pH unit to minimize, by a factor of 10, any local effects within the stomach that may produce areas of lower pH that might cause PPI degradation. A value of +1 log value is also supported by the observation that weak bases operate most efficiently at neutralizing acid beginning at +1 log value above the pKa.

For example, one would expect to encounter about 100–150 ml of 0.11 to 0.16N HCl in the adult fasting stomach, which is equivalent to about 12–24 mEq of HCl. Therefore, an equal amount of base will neutralize this acid. If about 12–24 mEq of sodium bicarbonate is employed as the buffer, the resulting pH will be left at the pKa of the conjugate acid of sodium bicarbonate (carbonic acid), which is about 6.14 or greater. This is greater than the lower limit of the pH_E for omeprazole of 4.6. Thus, administering 12–24 mEq of sodium bicarbonate with omeprazole protects greater than 95% of the drug when encountering 12–24 mEq of HCl. Because sodium bicarbonate complexes with HCl at a rate that exceeds the rate of interaction of omeprazole, it is considered a suitable buffer.

It should be noted that depending on age and disease, the amount of acid to be encountered can be significantly more or less than the 12–24 mEq range, but is generally from about 4 mEq to about 30 mEq.

Using magnesium oxide or magnesium hydroxide in an amount of 12 to 24 mEq also provides sufficient neutralizing capacity leaving the pH at approximately 7 (lowered only slightly by the minimal hydrolysis of magnesium). However, magnesium hydroxide is not rapid in onset and care should be taken to ensure that early degradation of the PPI does not occur. Early degradation can be avoided by making a tablet comprising two layers: an inner layer of PPI and sodium bicarbonate, and an outer layer of magnesium hydroxide dried gel or magnesium oxide with suitable disintegrant such that the magnesium oxide would rapidly disintegrate in the stomach. Alternatively, the inner layer can contain the magnesium buffer and the outer layer has the PPI and sodium bicarbonate.

Additionally, micronization of the slower acting buffer can be used to enhance its ability to combine with acid. Calcium carbonate (and many other calcium buffers) is a similar slower acting (compared to sodium bicarbonate) but potent buffer. Therefore, if used, it would be best suited in an outer layer of a tablet formulation with the inner layer comprising a rapid acting buffer with PPI (or vice versa). Alternatively, mixtures of the buffers can be employed for the outer layer. If developing a liquid formulation or a powder for reconstitution, a mixture of a rapid acting buffer and slower acting buffer can be used (e.g., sodium bicarbonate and magnesium oxide, respectively).

Modifications to the formulations may entail adjusting the pH of products with basic or acidic chemicals, including but not limited to, chemicals described throughout this application. Modifications of buffer pH based on the pH_E may or may not be performed in specific instances, depending upon species, age, disease and other variations between patients.

D. pKa and Solubility of PPIs

As mentioned above, the pKa of a given PPI indicates inherent stability with respect to acid degradation; the lower the pKa, the more stable the PPI. The solubility of the PPI will also dictate the rate at which the PPI complexes with, and is degraded by, acid. These two physicochemical characteristics (pKa and solubility) of the PPI interact with the physicochemical characteristics of the buffer(s) (pH, buffering capacity and rate of buffering action) in the presence of acid in the environment to determine the degradation of the PPI over time. The less soluble a PPI is in water, the lower the initial degradation when placed in an acidic environment. The following Table 11 elaborates on the time for 50% of drug to be degraded (t ½), pKa and solubility in water of several PPIs.

TABLE 11

PH	Pantoprazole sodium	Omeprazole	Lansoprazole	Rabeprazole sodium
1.2	4.6 min	2.8 min	2.0 min	1.3 min
5	2.8 hr	1.0 hr	1.1 hr	
5.1	4.7 hr	1.4 hr	1.5 hr	7.2 minutes
6	21 hr	7.3 hr	6.4 hr	
7	73 hr	39 hr	35 hr	
PKa	3	3.9	4.1	4.9
Solubility	very soluble	slightly soluble	very slightly soluble	Very soluble

Kromer W, et al. Differences in pH-Dependent Activation Rates of Substituted Benzimidazoles and Biological in vitro Correlates, PHARMACOLOGY 1998; 56:57–70.

Although pantoprazole sodium, with a pKa of 3, is inherently more stable in an acidic environment than other PPIs, it is also very soluble in water and thus could undergo

50% degradation in an acidic stomach with a pH of 1.2 in less than 5 minutes. Therefore, it is important for the buffer(s) used with pantoprazole sodium to interact with H+ ion (or other acidic substances) more rapidly than the pantoprazole sodium interacts with such acids and maintain the rapid complexation through the dwell time; otherwise, additional dosing of buffer may be required. The overall pH of the gastric contents should be kept at least at the pKa+0.7 (i.e., 3.7) from the time the PPI in solution comes into contact with the gastric acid continuing throughout the dwell time. Essential Buffers for liquid formulations of pantoprazole sodium include those buffers whose conjugate acids possess a pKa>3.7 and which are very soluble (e.g., potassium bicarbonate and sodium bicarbonate) Oral solid formulations likewise would require buffers whose conjugate acid possesses a pKa>3.7 and rapid complexation potential. Most magnesium, calcium and aluminum salts are not suitable unless the pantoprazole sodium is placed (with or without additional buffer) in an inner portion of a tablet or capsule with such antacids, and surrounded by a rapid acting buffer with a rapid disintegrant. Another formulation method for pantoprazole is to decrease its solubility such as by selecting a less soluble salt form or the non-salt form, pantoprazole.

Rabeprazole sodium is also very soluble in water and could undergo 50% degradation in an acidic stomach with a pH of 1.2 in less than 1.5 minutes. It is not very stable to acid degradation due to its higher pKa of 4.9. A suitable buffer(s) for rabeprazole sodium interacts with H+ ion (or other acidic substances) more rapidly than the rabeprazole sodium interacts with such acids to prevent early degradation, and should possess high neutralizing capacity to enable rabeprazole to survive through the dwell time. Sodium or potassium bicarbonate would be good choices in this instance.

Another option for rabeprazole sodium (as well as any sodium salt of a proton pump inhibitor, which would tend to be more soluble than the base form) is to reduce the solubility of rabeprazole sodium when in aqueous form such as using a less soluble salt form or using the non-salt form. This decreases early degradation because the rabeprazole must first undergo dissolution in water before it is degraded by acid. In this embodiment, the suitable buffer(s) for rabeprazole sodium should possess high neutralizing capacity to enable rabeprazole to survive through the dwell time.

For PPIs that possess high pKa's, such as rabeprazole sodium, a two-part liquid formulation can be utilized. The liquid part has the PPI and a high pH, but a low mEq buffering capacity. The liquid part is added to a second part that possesses a lower pH but a higher mEq buffering capacity. When these two parts are added together just prior to administration, a formulation with a lower pH and a higher buffering capacity is produced which will neutralize stomach acid but not be too caustic to tissues. Examples of such formulations are provided below.

For highly soluble PPIs, the formulation may be produced in a solid dosage form such as a tablet, capsule or powder with a buffer(s), which disintegrate and reach solution at a rate that exceeds the PPI and thereby provides the Essential pH for protection of the PPI prior to its dissolution and interaction with the acid in the environment. Further, the tablet or capsule may be formulated to possess an outer portion of buffer and an inner portion comprising PPI, or a blend of PPI and buffer. Additional methods include formulating the buffer in a smaller particle size (e.g., micronized) and the PPI in a larger particle size. This results in the disintegration of the buffer component prior to disintegration of the PPI component. All of these methods of formulation aim to create an environment of stability for the PPI during the dwell time.

The dosage form may affect the suitability of a buffer for use in a formulation. For example, magnesium oxide is a buffer with high buffering capacity but slow onset when formulated as a tablet. However, when formulated as a powder, or a tablet of low compression, or with tablet disintegrants such as pregelatinized starch, it disintegrates more rapidly.

Omeprazole base is only slightly soluble in water and, as such, less of the drug is subject to early and continued degradation. The soluble portion of omeprazole is vulnerable to early degradation in the gastric environment. Dissolution of the remaining insoluble portion is expected to occur within minutes of encountering the water of the gastric secretions. This dissolution time provides some protection against early degradation provided that relatively low volumes of water are used during delivery or in the product formulation. After several minutes in the gastric environment, upon complete dissolution, omeprazole could undergo 50% degradation in less than 3 minutes. Omeprazole is moderately stable owing to its pKa of 3.9. A suitable buffer(s) for omeprazole is rapid acting and possesses at least moderate neutralizing capacity to enable omeprazole to survive through the dwell time.

As used herein, "rapid acting" in the context of a buffer means a buffer that raises the pH of the environment to greater than or equal to the pH_E of a particular PPI in a time sufficient to prevent significant degradation of the PPI. In one embodiment, the rapid acting buffer raises the pH to at least the pKa of the PPI plus 0.7 log value within 10 minutes.

Preferred buffer(s) produce an environment where the Resultant pH of the environment is equal to or greater than the Essential pH such that: (1) the onset of pH change to equal to or greater than the pH_E+0.7 begins before the acid-induced degradation of the PPI occurs, and (2) the Resultant pH at or greater than the pH_E+0.7 lasts throughout the dwell time, which is typically a minimum of 30 minutes in the case of gastric emptying for an adult. It is desirable that the buffer be rapid acting to minimize early acid-induced degradation. The most rapid acting buffers are water soluble (or soluble in the environment). High solubility, however, is not an absolute necessity as magnesium oxide and calcium carbonate, both only slightly soluble, are capable of significant complexation with gastric acid albeit at a slower rate. If a dry formulation is used, such as a tablet, the particle size of the buffer(s) can be reduced to enhance the dissolution rate while the particle size of the PPI can be increased. Disintegrants can be added to enhance the availability of poorly soluble buffers.

Lansoprazole base is very slightly soluble in water and, as such, less of the drug is subject to early degradation. The soluble portion is vulnerable to early degradation. Dissolution of the remaining insoluble portion is expected to occur within several minutes of encountering the water of the gastric secretions. This dissolution time provides some protection against early degradation provided that relatively low volumes of water are used for delivery or in the product formulation. After several minutes, upon complete dissolution, lansoprazole could undergo 50% degradation in 2 minutes. Lansoprazole is moderately stable owing to its pKa of 4.1. A suitable buffer(s) for lansoprazole should be rapid acting, and should possess moderate to high neutralizing capacity to enable lansoprazole to survive through the dwell time. The pH of the gastric contents (or other environment) should be kept at greater than about 4.8 from the time the PPI in solution comes into contact with the gastric acid continuing throughout the dwell time.

E. Calculating the Acid Neutralizing Capacity of Buffers

The acid neutralizing capacity ("ANC") of soluble buffers may be used to assist in selecting a preferred amount of buffer(s) needed to provide the EBC. The ANC uses both the formula weight (FWt.) and the valence to determine buffering capacity.

An example of an ANC calculation for sodium bicarbonate is as follows:

Sodium Bicarbonate, $Na^+HCO_3^-$, FWt.=84, valence=1. The conversion equation from equivalent weight to grams is:

(Equivalent Weight ("EW"))(1/1000 mmol)(1 mmol/1 mEq)=grams of $NaCHO_3$

EW=(FWt.)/(valence)=84/1=84 g/mol.

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 mEq)=0.34 g $NaHCO_3$ needed for 4 mEq of buffering capacity.

Accordingly, for 10 mEq, one needs 0.840 g $NaHCO_3$, and for 30 mEq, 2.52 gm is required. The range of 4–30 m Eq is used because that is the range of mEq of acid to be encountered in most patients.

The ANCs of other buffers are similarly calculated. ANC determinations are from Drake and Hollander, *Neutralizing Capacity And Cost Effectiveness Of Antacids*, Ann Intern. Med. 109:215–17 (1981). Generally, the formulations of the present invention need about 4 to about 30 mEq of buffering capacity although higher amounts could be used in some patients.

Sodium bicarbonate in solution possesses a pH>pH_E of omeprazole and rapidly neutralizes acidic environments. As stated above, rapid complexation with HCl is a desirable characteristic of an Essential Buffer. Ideally, but not necessarily required as indicated in formulations that contain a tablet in a tablet, the Essential Buffer complexes with the acid at a faster rate than the PPI it is intended to protect.

In selecting Essential Buffers, a knowledge of buffering capacity is also useful since they possess differing pHs at various concentrations. The magnitude of the resistance of a buffer to pH changes is referred to as buffer capacity (Beta). It has been defined by Koppel, Spiro and Van Slyke as the ratio of the increment of strong acid (or base) to the change in pH brought about by addition of acid. The following formula is used to measure buffer capacity: Buffer capacity=the increment (in gram equivalents per liter) of strong acid added to the buffer solution to produce a pH change (change as measured in absolute terms), or buffer capacity=change in acid/change in pH. Improvements in the formula have been made to improve the precision, and these form the basis for mathematical comparison of buffers for consideration. See Koppel, BioChem, Z. (65) 409–439 (1914), Van Slyke, J. Biol. Chem. 52:525 (1922).

When the PPI/buffer formulation is placed in the environment, the PPI is subject to degradation by the acid in that environment. As depicted in FIG. 9, PPI solubility, the pKa of the PPI, and the amount and concentration of acid (H+ ion) encountered in the environment are variables that can be used to determine the appropriate candidate as an Essential Buffer. Early degradation occurs when the soluble portion of the PPI (that portion available for immediate interaction with H+ ion) undergoes hydrolysis by H+ ion. PPIs differ in their solubility and, therefore, those that are more soluble have a potential for a higher portion of PPI degraded by early interaction with H+ ion. The pKa of the PPI and the pH of the environment of the stomach (or other site of interest) after addition of the PPI/buffer formulation (Resultant pH) can be used to determine the desirable Essential Buffer. By measuring the Resultant pH over time, the pH data versus time can be plotted as seen in FIG. 9. The graph of pH over time can then be used to evaluate various buffers.

Such a graph can be developed for a potential buffer or buffer combination using the Rossett-Rice test (Rosset N E, Marion L: *An In Vitro Evaluation Of The Efficacy Of The More Frequently Used Antacids With Particular Attention To Tablets*. Antacids 26: 490–95 (1954), modified with continual addition of simulated gastric fluid. See USP XXIII, *The United States Pharmacopeia*, 23rd Revision, United States Pharmacopeia Convention, Inc. Briefly, the test employs 150 mL of simulated gastric fluid consisting of 2 Gm of sodium chloride and 3.2 Gm of pepsin, which are dissolved in 7 mL of 1N HCl, q.s. to 1000 mL with distilled water. The pH of the simulated gastric fluid is 1.2. A container of 150 mL of this fluid is stirred at 300 rpm±30 rpm with a magnetic stirrer and kept at 37.1° C. A pH electrode is kept in the upper region of the solution. The test buffer or the subject formulation is added to the container to start the evaluation. At 10 minutes, a continuous drip of simulated gastric fluid is added to the test container at a rate of 1.6 ml/min to simulate gastric secretion. Approximately 1.6 mL/min is removed from the test container to keep the volume in the test container constant. The evaluation continues for at least 90 minutes.

This methodology allows for a dynamic evaluation of buffering capacity in a model designed to mimic a fasting human stomach. It has been described in part for use in evaluating antacids by Beneyto J E, et. al., *Evaluation of a New Antacid, Almagate*, Arzneim-Forsch/Drug Res 1984; 34 (10A): 1350–4; Kerkhof N J, et al, *pH-Stat Tiration of Aluminum Hydroxide Gel*, J. Pharm. Sci. 1977; 66: 1528–32.

Using this method, a pH tracing can be developed for evaluating buffers as well as finished products. In addition, a sample of the test solution can be taken during the experiment to evaluate the extent of PPI degradation at various times. Those buffers with a suitable profile as exemplified in FIG. 9 able to maintain pH greater than or equal to PH_E for 30 minutes or greater, can be considered suitable Essential Buffers. In one embodiment, as depicted in FIG. 9, the pH was recorded over 10 second intervals.

A number of buffers may be applicable for use as Essential Buffers. Therefore, once an Essential Buffer is chosen, the amount necessary to provide the EBC is calculated. As used herein, the EBC is the buffering capacity, or amount of alkaline buffer, included in the dose and calculated to maintain the Essential pH range and thereby protect any substituted benzimidazole PPI in the gastric (or other) environment. In patients requiring continuing PPI administration (e.g. daily), more buffering capacity may be necessary with the first dose or first few doses than with subsequent doses because the PPI may encounter more acid with the initial doses. Subsequent doses will require less buffering capacity because the initial PPI doses will have reduced gastric acid production. The EBC could therefore be reduced in subsequent doses. The product's buffering capacity may be formulated as desired, for instance with respect to patient age, gender or species.

Experimental data from adult human subjects showed an effective EBC range of a first dose of omeprazole to be about 4 to about 20 mEq ("EBC-O range") of sodium bicarbonate, with a range of about 12 to about 25 mEq suitable in most instances. Subsequent doses of omeprazole require less EBC, with a range of about 4 to 15 mEq sodium bicarbonate. In one embodiment, this latter EBC range proved optimal for an omeprazole suspension administered to patients with varying degrees of gastrointestinal transit and acid output,

based on a knowledge of basal and maximal acid outputs of 2 and 25 mEq/hour, respectively. These studies have been reported in Phillips J. O. et al., Crit. Care Med. 1996; Lasky et al., J. Trauma 1998.

Based on the EBC-O range, the above ANC calculation can be employed. Additionally, it is expected to encounter about 100–150 mL of 0.1 N HCl (equating to about 12–24 mEq of acid) in a fasting stomach. Variations in the acid encountered in the environment will affect the Essential Buffering Capacity required. The above EBC ranges relate to adult patients. Children, however, produce less acid per unit time in comparison to adults. Therefore, depending on the patient population, the amount of Essential Buffering Capacity required may be altered.

Numerous references are available to assist the skilled artisan in identifying a suitable buffer companion with a PPI to determine the desirable characteristics stated herein. See, e.g., Holbert, et. al., *A Study of Antacid Buffers: I. The Time Factor in Neutralization of Gastric Acidity*, J. Amer. Pharm. Assn. 36: 149–51 (1947); Lin, et. al., *Evaluation of Buffering Capacity and Acid Neutralizing pH Time Profile of Antacids*, J. Formosa Med. Assn. 97 (10) 704–710 (1998); *Physical Pharmacy*, pp 169–189; *Remington: The Science and Practice of Pharmacy* (2000).

F. The Desirable Volume

The Desirable Volume ("DV") of a PPI dose may affect PPI delivery to and action upon parietal cell proton pumps. The DV of a dose is partly based on the EBC. For liquid formulations, a desirable volume should deliver sufficient buffer to act as an antacid to neutralize a substantial amount of gastric or other acids. For solid formulations such as tablets, a nominal amount of water or other fluid will be consumed to aid in swallowing the tablet. Liquid preparations of the present invention use volumes as small as about 2 ml or in excess of about 60 ml. Volumes smaller than 2 ml and larger than 60 ml are contemplated, and may be used as desired to suit individual patients, such as those of advanced or very young age or of different species. Very large volumes may lead to higher amounts of less soluble PPIs (e.g., omeprazole, lansoprazole base forms) going into solution, which could result in vulnerability to early degradation.

For instance, volumes smaller than about 2 ml may be used in newborns or premature infants, or in small animals, because of their smaller stomach size. Also, a large DV may be required for doses formulated with dilute buffer concentrations, to achieve the EBC. The relationship between the EBC and DV is in part shown below:

If EBC(mg buffer)=Buffer conc.(mg/ml)×DV(ml),

then DV(ml)=EBC(mg)/Buffer conc.(mg/ml).

Alternatively, mEq can be substituted for mg in the formula.

G. Secondary Components of the Formulations

Secondary components are not required but may be used to enhance the pharmacological action or as pharmaceutical aids. Secondary components may include, but are not limited to, parietal cell activators and other ingredients. Parietal cell activators, as discussed above, are compounds that produce an increase in proton pump activity such that proton pumps are relocated from storage sites of the parietal cell, i.e. tubulovesicles, to the site of H+, K+ exchange at the secretory canaliculus. A parietal cell activator may also serve other functions. For example, sodium bicarbonate is an Essential Buffer as well as a parietal cell activator, chocolate is a parietal cell activator and a flavoring agent, and aspartame, which contains phenylalanine, is a sweetener as well as a parietal cell activator.

Parietal cell activators can be divided into four groups: 1) rapid acting buffers that are weak bases, strong bases or combinations thereof that also produce a rapid onset of effect (the pH drops rather suddenly after the buffer is exhausted; these buffers typically cause the pH of the stomach to rise to above 5); 2) amino acids, protein hydrolysates and proteins; 3) calcium containing compounds such as calcium chloride or calcium carbonate; and 4) compositions such as coffee, cocoa, caffeine and peppermint.

The other ingredients comprise components of a formulation that are secondary to the primary components. Other ingredients include, but are not limited to, thickening agents, flavoring agents, sweeteners, antifoaming agents (such as simethicone), preservatives, antibacterial or antimicrobials agents (such as cefazolin, amoxicillin, sulfamethoxazole, sulfisoxazole, erythromycin and other macrolides such as clarithromycin or azithromycin), and Secondary Essential Buffers.

Desirable flavoring agents may be added to the dosage forms, and may or may not need to be buffered to the pH_E. Flavoring agents with pH values inherently suitable to the range of pH_E values of PPIs include, but are not limited to, apple, caramel, meat, chocolate, root beer, maple, cherry, coffee, mint, licorice, nut, butter, butterscotch, and peanut butter flavorings, used alone or in any combination. Similarly, all substances included in the formulation of any PPI product, including but not limited to, activators, antifoaming agents, potentiators, antioxidants, antimicrobial agents, chelators, sweeteners, thickeners, preservatives, or other additives or substances may be buffered to the pH_E.

H. Examples Utilizing the Calculations

The pH_E, the EBC, and the DV of a PPI dose may affect PPI delivery to, and action upon, parietal cell proton pumps. The following calculations tailor an Essential Buffer dose for any substituted benzimidazole PPI to promote PPI efficacy in an oral administration.

Example 1

To deliver a 20 mg dose of omeprazole (pKa=3.9) in sodium bicarbonate:

Step 1: The pH_E of omeprazole=pKa of omeprazole+0.7=4.6. The SRF of omeprazole=pH_E to 10.9=4.6 to 10.9. At a Formulation pH of 4.6 to 10.9, the conjugate base of sodium bicarbonate (carbonic acid) has a pKa of 6.14. Therefore, an amount of sodium bicarbonate equivalent to the amount of acid to be encountered would produce a pH of 6.14, which is within the SRF of 4.6 to 10.9. Sodium bicarbonate would make a suitable choice as a buffer.

Step 2: The EBC=4 to 30 mEq buffering capacity equivalent.

Step 3: To determine the amount of sodium bicarbonate to administer with the omeprazole, the ANC for sodium bicarbonate is calculated. The ANC for sodium bicarbonate (MW=84 for 4–30 mEq)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC)

EW=MW/(valence)=84/1=84 g/mol

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.34 g to 2.52 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=Essential Buffer (EB) (mg)/Buffer conc. (mg/ml) Buffer conc.=EB/DV=340 mg to 2520 mg/20 ml=17 mg/ml to 126 mg/ml.

Therefore, for 20 mg of omeprazole to be adequately buffered in 20 ml of solution, the concentration of sodium bicarbonate should be 17 to 126 mg/ml.

Example 2

To deliver a 20 mg dose of omeprazole (pKa=3.9) in dibasic sodium phosphate:

Step 1: The pH_E of omeprazole=pKa of omeprazole+0.7. The SRF of omeprazole=(3.9+0.7) to 10.9=4.6 to 10.9.

Step 2: The EBC=4 to 30 mEq buffering capacity equivalent.

Step 3: To determine the amount of dibasic sodium phosphate to administer with the omeprazole, the ANC for dibasic sodium phosphate is calculated. The ANC for dibasic sodium phosphate (MW=142)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC).

EW=MW/(valence)=142/2=71 g/mol.

(71 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.28 g to 2.13 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml)

Buffer conc.=EB/DV=280 mg to 2130 mg/20 ml=14 mg/ml to 107 mg/ml.

Therefore, for 20 mg of omeprazole to be adequately buffered in 20 ml of solution, the concentration of dibasic sodium phosphate should be 14 to 107 mg/ml. The pka of disodium phosphate is 7.21. Therefore, an amount of disodium phosphate equivalent to the amount of acid to be encountered would produce a pH of approximately 7.2. Thus, disodium phosphate would make a suitable choice as a buffer.

Example 3

To deliver a 30 mg dose of lansoprazole (pKa=4.1) in sodium bicarbonate:

Step 1: The pH_E of lansoprazole=pKa of lansoprazole+0.7. The SRF of lansoprazole=(4.1+0.7) to 10.9=4.8 to 10.9.

Step 2: The EBC=4–30 mEq buffering capacity equivalent.

Step 3: To determine the amount of sodium bicarbonate to administer with the lansoprazole, the ANC for sodium bicarbonate is calculated. The ANC for sodium bicarbonate (MW=84)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC)

EW=MW/valence=84/1 g/mol

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.34 g to 2.52 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml)

Buffer conc.=EB/DV=340 mg to 2520 mg/20 ml=17 mg/ml to 126 mg/ml.

Therefore, for 30 mg of lansoprazole to be adequately buffered in 20 ml of solution, the concentration of sodium bicarbonate should be about 17 to about 126 mg/ml.

Example 4

To deliver a 40 mg dose of pantoprazole (pKa=3) in sodium bicarbonate:

Step 1: The pH_E of pantoprazole=pKa of pantoprazole+0.7. The SRF of pantoprazole=(3+0.7) to 10.9=3.7 to 10.9.

Step 2: The EBC=4–30 mEq buffering capacity equivalent.

Step 3: To determine the amount of sodium bicarbonate to administer with the pantoprazole, the ANC for sodium bicarbonate is calculated. The ANC for sodium bicarbonate (MW=84)=(EW)(1/1000 mmol)(1mmol/1 mEq)(EBC)

EW=MW/(valence)=84/1 g/mol

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.34 g to 2.52 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml)

Buffer conc.=EB/DV=340 mg to 2520 mg/20 ml=17 mg/ml to 126 mg/ml.

Therefore, for 40 mg of pantoprazole to be adequately buffered in 20 ml, the concentration of sodium bicarbonate should be about 17 to 126 mg/ml.

Example 5

To deliver a 20 mg dose of rabeprazole (pKa=5) in sodium phosphate dibasic:

Step 1: The PH_E of rabeprazole=pKa of rabeprazole+0.7. The SRF of rabeprazole=4.9+0.7) to 10.9=5.6 to 10.9.

Step 2: The EBC=4–30 mEq buffering capacity equivalent.

Step 3: Therefore, to determine the amount of sodium phosphate dibasic to administer with the rabeprazole, the ANC for potassium sodium dibasic is calculated. The ANC for sodium phosphate dibasic (duohydrate) (MW=174)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC)

EW=MW/valence=178/1 g/mol

(178 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 20 mEq)=0.712 g to 5.34 g sodium phosphate dibasic.

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml).

Buffer conc.=EB/DV=0.712 g to 2 g/20 ml=35.6 mg/ml to 100 mg/ml. In this case, the solubility of disodium phosphate would limit the amount that could be dissolved in 20 mL. Obviously, this would exceed the solubility of disodium phosphate (sodium phosphate dibasic). Therefore, for 20 mg of rabeprazole to be adequately buffered in 20 ml of solution, the concentration of sodium phosphate dibasic should be about 35.6 mg/ml to 100 mg/ml at a pH range of about 6.9 to 10.9. The pka of disodium phosphate is 7.21. Thus, an amount of disodium phosphate equivalent to the amount of acid to be encountered would produce a pH of approximately 7.2. Accordingly, disodium phosphate would make a suitable choice as a buffer.

It should be noted that the suitability of buffers relates to their use immediately after mixing. In order to enhance the shelf-life, higher pH values would be anticipated within the range of acceptable pH_E for a given PPI. As an example, rabeprazole suspensions containing various buffers were evaluated for color change because degradation of PPIs results in a color change to brown or black. All buffer suspensions started out white in color. After 2 weeks the following observations were made:

20 mg Rabeprazole in Various Buffers Stored Under Refrigerated Conditions As Suspensions

Buffer	Original Color	Color 14 days	pH at 14 days
Sodium bicarbonate 800 mg/10 mL	white	brown	8.3
Disodium phosphate 800 mg/10 mL	white	white	10.3
Disodium phosphate 700 mg; Trisodium phosphate 100 mg/10 mL	white	white	10.5

Similar calculations may be performed for any substituted benzimidazole PPI and appropriate buffer(s) including, but

not limited to, those exemplified above. One skilled in the art will appreciate that the order of the above steps is not critical to the invention. The above calculations may be used for formulations comprising one or more PPI and one or more buffers.

I. Veterinary Formulations

Horses produce stomach acid continuously throughout the day. It is the basal acid secretion from the stomach in the absence of feeding that is responsible for the erosion of the squamous mucosa in the stomach and ulcers. Horses on pasture normally secrete a continuous supply of saliva, which buffers the stomach acid. When horses are being ridden regularly, trained for shows or prepared for sales, they are usually kept in stalls much of the day. Under these conditions, the natural salivary buffering mechanism is disrupted and acid indigestion often results.

Almost 40 to about 100 mEq of buffer capacity should provide approximately 2.5 hours of neutralization for a horse. The usual dose of omeprazole ranges from 0.7 to 1.5 mg/kg/day (doses up to 4 mg/kg/day may be required) and a typical weight for a horse is 500 kg. Similar dosages are expected for rabeprazole and lansoprazole.

Dogs can also suffer from ulcers and their dosage is approximately 1 mg/kg/day. The following formulations are designed for use in horses but smaller amounts can be used in dogs with an EBC of 10 to 20 mEq.

Formulation 5: Veterinary Formulation of Omeprazole	
This formulation is particularly well suited for animals rather than humans because the dose of PPI is high.	
EBC = 75 mEq	
Essential pH (omeprazole pKa = 3.9 + 0.7 ≧ 4.6)	
PPI: Omeprazole powder	500 mg (a range of 350 to 700 mg)
Primary Essential Buffer(s):	
Sodium bicarbonate	5 g (59.5 mEq)
Dibasic sodium phosphate (anhydrous)	2 g (14 mEq)
Optional Secondary Essential Buffer(s):	
Tribasic sodium phosphate	200 mg. (1.2 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering effect.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as guar gum 350 mg, artificial maple flavor powder 100 mg, thaumatin powder 10 mg (to mask the bitterness of omeprazole), and sucrose 25 Gm. Q.s. to 100 mL with distilled water to achieve a final omeprazole concentration of 5 mg/mL. Different volumes of water may be added to achieve omeprazole concentrations ranging from about 0.8 to about 20 mg/mL.

Alternatively, this formulation may be divided into two parts. The dry part may be reconstituted with the liquid part at the time of use.

Formulation 6: Veterinary Formulation of Lansoprazole	
Essential pH (lansoprazole pKa = 4.1 + 0.7 ≧ 4.8)	
EBC = 71.4 mEq	
PPI: Lansoprazole powder	750 mg

-continued

Formulation 6: Veterinary Formulation of Lansoprazole	
Primary Essential Buffer(s):	
Sodium bicarbonate	6 g (71.4 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering effect.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as xanthan gum 300 mg, artificial peanut butter flavor powder 100 mg, and sucrose 35 Gm. Q.s. to 100 mL with distilled water to achieve a final lansoprazole concentration of 7.5 mg/mL. The suspension should be refrigerated after reconstitution. Different volumes of water may be added to achieve lansoprazole concentrations ranging from 0.8 to 20 mg/mL.

Alternatively, this formulation may divided into two parts. The dry part may be reconstituted with the liquid part at the time of use.

Formulation 7: Veterinary Formulation of Lansoprazole	
Essential pH (lansoprazole pKa = 4.1 + 0.7 ≧ 4.8)	
EBG = 63.3 mEq	
PPI:	
Lansoprazole powder	750 mg
Primary Essential Buffer(s)	
Sodium bicarbonate	5 g (59.5 mEq)
Secondary Essential Buffer(s):	
Sodium carbonate	400 mg* (3.8 mEq)

(*Any Secondary Essential Buffer(s) may be added to adjust pH for desired stability and additive antacid or buffering effect.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl methyl cellulose 300 mg, artificial maple flavor 100 mg, and sucrose 35 Gm. Q.s. to 100 mL with distilled water to achieve a final lansoprazole concentration of 7.5 mg/mL. Different volumes of water may be added to achieve lansoprazole concentrations ranging from 0.3 to 20 mg/mL.

Alternatively, this formulation may divided into two parts. The dry part may be reconstituted with the liquid part at the time of use.

Formulation 8: Veterinary Formulation of Esomeprazole Magnesium	
Essential pH (esomeprazole pKa = 3.9 + 0.7 ≧ 4.6)	
EBC = 53.2 mEq	
PPI:	
Esomeprazole magnesium powder	500 mg
Primary Essential Buffer(s):	
Sodium bicarbonate	5 g (47.6 mEq)
Dibasic sodium phosphate	800 mg (5.6 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl cellulose 300

mg, artificial butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water to achieve a final esomeprazole concentration of 7.5 mg/mL. Different volumes of water may be added to achieve esomeprazole concentrations ranging from 0.8 to 20 mg/mL.

Formulation 9: Veterinary Formulation of Pantoprazole Sodium or Pantoprazole Base Powder

Essential pH (pantoprazole sodium pKa = 3 + 0.7 ≧ 3.7)	
EBC = 53.8 mEq	
Pantoprazole sodium or pantoprazole powder	1000 mg
Primary Essential Buffer(s):	
Sodium bicarbonate	4 g (47.6 mEq)
Secondary Essential Buffer(s):	
Trisodium phosphate	1000 mg* (6.2 mEq)

(*Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl cellulose 300 mg, artificial butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water to achieve a final pantoprazole concentration of 10 mg/mL. Different volumes of water may be added to achieve esomeprazole concentrations ranging from 0.2 to 20 mg/mL.

Formulation 10: Veterinary Formulation: Buffer Base Without PPI

EBC = 71.4 mEq	
Primary Essential Buffer:	
Sodium bicarbonate	6 g 71.4 mEq
Optional Secondary Essential Buffer:	
Tribasic sodium phosphate	1000 mg*

(* Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl cellulose 300 mg, artificial butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water. A PPI or other acid-labile drug may be added by the compounding pharmacist selected from available PPIs or acid-labile drugs from powder or enteric-coated oral solid dosage forms. Different volumes of water may be added to achieve PPI concentrations ranging from 0.8 to 20 mg/mL. If other acid labile drugs are employed, the range of concentrations would be as required to deliver the normal dosage in an acceptable volume of 1 mL to 30 mL. The amount of buffer required to protect the drug in question will also determine the minimal feasible volume. This formulation may be in the form of a one-part product (liquid or dry) or a two-part product (liquid and dry), for examples. In the two-part example, the drug to be added to the formulation may be added to the dry formulation and the liquid part may be added at the time of use, or the drug may be added to the liquid portion which would be buffered to a pH above that required for disintegration of enteric-coated drug formulations (typically pH of 6.8 or greater).

For all of the veterinary and human oral dosage forms disclosed herein, sweeteners, parietal cell activators, thickeners, preservatives, and flavoring agents may also be added. Sweeteners include but are not limited to corn syrup, simple syrup, sugar, thaumatin, and aspartame. Thickeners include but are not limited to methylcellulose, xanthan gum, carrageenan, and guar gum. Preservatives may be added to retard spoilage and include but are not limited to sodium benzoate, methylparaben and propylparaben. Flavoring agents in these formulations include but are not limited to apple, caramel, maple, peanut butter, meat, etc.

J. Other Formulations

For all formulations herein, the total amount of Essential Buffer may range from about 4 mEq to about 30 mEq per dose.

Formulation 11: Oral Buffer Complex Without PPI (for general use to protect acid labile drugs) Multidose Composition

Primary Essential Buffer:	
Dibasic sodium phosphate or sodium bicarbonate	10 g (range 2 g to 10 g)
Optional Secondary Essential Buffer: Tribasic sodium phosphate or sodium carbonate	200 mg
Other ingredients:	
Sucrose	26 g
Maltodextrin	2 g
Cocoa processed with alkali	1800 mg
Corn syrup solids	6000 mg
Sodium caseinate	100 mg
Soy lecithin	80 mg

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet. Preservatives may be added to retard spoilage and include but are not limited to sodium benzoate, methylparaben, and propylparaben. Thickeners such as xanthan gum, guar gum, or hydroxymethyl propyl cellulose can be flavoring agents in these formulations include chocolate, caramel, maple, butter pecan and other flavorings as have been outlined previously. Different volumes of water may be added to achieve PPI concentrations ranging from 0.8 to 20 mg/mL.

Weigh out approximately 60 g of the formulation. Add PPI (or other acid-labile drug) typically in the amount equivalent to 10 doses (range 1 dose to 30 doses).

Q.s. to 100 mL with distilled water.

Formulation 12: Oral Buffer Complex Without PPI For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Primary Essential Buffer:	
Sodium bicarbonate	5 g (range 2 g to 10 g) (59.5 mEq)
Optional: Secondary Essential Buffer	
None*	
Other ingredients	
Sucrose	26 g
Maltodextrin	2 g
Cocoa processed with alkali	1800 mg

-continued

Formulation 12: Oral Buffer Complex Without PPI For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example	
Corn syrup solids	6000 mg
Soy lecithin	80 mg

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)
Note that cocoa is a parietal cell activator.

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add PPI (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses).

Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve PPI concentrations ranging from 0.8 to 20 mg/mL.

Formulation 13: Buffer Complex Without PPI For General Use to Protect Acid Labile Drugs; Protein Free, Lactose Free Multidose Example	
PPI:	
None (to be added later, e.g. by compounding pharmacist)	
Primary Essential Buffer(s):	
Sodium bicarbonate	8 g (range 2 g to 10 g)
Other ingredients:	
Sucrose	26 g
Maltodextrin	2 g
Corn syrup solids	6000 mg
Partially hydrogenated soybean oil	400 mg
Dipotassium phosphate	300 mg
Caramel flavor	270 mg
Soy lecithin	80 mg
Sodium silico aluminate	20 mg
Titanium dioxide	10 mg

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet.

Optional Secondary Essential Buffer:

Tribasic sodium phosphate 1000 mg

Weigh out approximately 60 g of the formulation. Add PPI (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve PPI concentrations ranging from 0.3 to 20 mg/mL.

Formulation 14: Buffer Complex Without PPI For General Use to Protect Acid Labile Drugs: Protein Free, Multi-Dose Example	
PPI:	
None (to be added later, e.g. by compounding pharmacist)	
Primary Essential Buffer(s):	
Dibasic sodium phosphate	8 g (range 2 g to 10 g)
Other ingredients:	
Sucrose	26 g

-continued

Formulation 14: Buffer Complex Without PPI For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example	
Maltodextrin	2 g
Butterscotch flavor	270 mg
Corn syrup solids	6000 mg

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet.

Weigh out approximately 60 g of the formulation. Add PPI (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve PPI concentrations ranging from 0.8 to 20 mg/mL.

Formulation 15: Buffer Complex Without PPI For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example	
PPI:	
None (to be added later, e.g. by compounding pharmacist)	
Primary Essential Buffer(s):	
Sodium bicarbonate	8 g (range 1 g to 10 g)
Secondary Essential Buffer(s):	
Trisodium phosphate	1.5 g (range 0 g to 5 g)
Other ingredients:	
Sucrose	26 g
Maltodextrin	2 g
Butterscotch flavor	270 mg
Corn syrup solids	6000 mg

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add PPI (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve PPI concentrations ranging from 0.8 to 20 mg/mL.

Formulation 16: One Phase Lansoprazole 30 mg Tablet Lansoprazole has a pKa of 4.1; thus, the Essential pH = 4.1 + 0.7 ≧ 4.8 Examples of buffers that produce a solution with pH 4.8 or greater and produce the Essential Buffering Capacity include, but are not limited to, sodium bicarbonate, sodium carbonate, dibasic sodium phosphate, and dipotassium phosphate.	
Enough powder for 11 tablets is weighed out:	
PPI:	
Lansoprazole powder	330 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	5500 mg
Dibasic sodium phosphate	2200 mg

The resultant powder is thoroughly mixed. Then 720 mg of the homogeneous mixture is poured into a tablet reservoir

(½ inch diameter) and pressed through a full motion of the press as is known in the art. The resultant tablet contains:

Lansoprazole	30 mg
Sodium bicarbonate USP	500 mg
Disodium hydrogen phosphate	200 mg

The tablet contains 6 mEq sodium bicarbonate and 1.4 mEq dibasic sodium phosphate. Variations in this tablet may include a tablet containing all dibasic sodium phosphate or all sodium bicarbonate or other buffers from the Essential Buffers list. The amount of Effective Buffer Capacity per tablet may range from as little as about 4 mEq to as much as about 30 mEq.

Additional tablet disintegrants such as croscarmelose sodium, pregelatinized starch, or providone, and tablet binders such as tapioca, gelatin, or PVP may be added. Further, a film coating may be placed on the tablet to reduce the penetration of light and improve ease of swallowing.

Formulation 17:
One Phase Omeprazole 20 mg Tablet
Omeprazole has a pKa of 3.9; thus, the Essential pH = 3.9 + 0.7 ≧ 4.6
Examples of buffers that are soluble at pH 4.6 or greater include, but are not limited to, sodium bicarbonate, sodium carbonate, disodium hydrogen phosphate (dibasic sodium phosphate), and dipotassium phosphate.

Enough powder for 11 tablets is weighed out:	
PPI:	
Omeprazole powder USP	220 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	6500 mg
Magnesium oxide powder	1650 mg
Croscarmelose sodium	300 mg

The resultant powder is thoroughly mixed. Then 788 mg of the homogeneous mixture is poured into a tablet reservoir (½ inch diameter) and pressed through a full motion of the press as is known in the art. The resultant tablet contains:

Omeprazole USP	20 mg
Sodium bicarbonate USP	590 mg
Magnesium oxide	150 mg
Croscarmelose sodium	27.27 mg

The tablet contains 7 mEq sodium bicarbonate and 3.75 mEq magnesium oxide. The amount of Effective Buffer Capacity may range from as little as about 4 mEq to as much as about 30 mEq. The tablet excipients, tablet binders, and film coating of Formulation 16 may also be added.

Formulation 18:
One Phase Omeprazole 40 mg Tablet

Enough powder for 11 tablets is weighed out:	
PPI:	
Omeprazole powder USP	440 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	6500 mg

-continued

Formulation 18:
One Phase Omeprazole 40 mg Tablet

Magnesium oxide	1650 mg
Pregelatinized starch	500 mg

The resultant powder is thoroughly mixed. Then 826 mg of the homogeneous mixture is poured into a tablet reservoir (½ inch diameter) and pressed through a full motion of the press as is known in the art. The resultant tablet contains:

Omeprazole USP	40 mg
Sodium bicarbonate USP	590 mg
Magnesium oxide	150 mg
Pregelatinized starch	45.45 mg

The tablet contains 7 mEq sodium bicarbonate and 3.75 mEq magnesium oxide. The amount of Effective Buffer Capacity may range from as little as 4 mEq to as much as 30 mEq. The tablet excipients, tablet binders, and film coating of Formulation 16 may also be added.

Esomeprazole magnesium or other proton pump inhibitors which are of low solubility (such as the base forms) may be used in place of omeprazole or lansoprazole in the above formulations. The tablet excipients, tablet binders, and film coatings of Formulation 16 may also be added. In addition, powders of any of the formulations disclosed herein may be manufactured by thoroughly mixing the powders as when making tablets and omitting the pressing of the tablets. The powder is packaged in a suitable container protecting the formulation from air moisture and light such as a foil pack or sachet. When added to a volume of water (e.g. 3 to 20 mL) the formulation may be taken orally or administered down a feeding or NG tube, etc. Flavoring agents such as are outlined in the above formulations may be used, for example, carmel flavor 0.1% w/w. For bitter tasting PPIs such as pantoprazole, omeprazole, esomperazole and rabeprazole, the use of thaumatin in a quantity of 5 to 10 ppm may be useful in masking the bitterness. Sweeteners such as sucrose or aspartame may also be employed. Tablet disintegrants such as croscarmelose sodium and glidants such as magnesium stearate may additionally be used.

Formulation 19: Omeprazole Powder Formulations (single dose)

PPI:	
Omeprazole powder USP (or esomeprazole magnesium).	20 mg or 40 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP powder (60 micron)	1000 mg
Magnesium oxide USP powder	500 mg
Optional Secondary Essential Buffer(s):	
Tribasic sodium phosphate	200 mg*
Other ingredients:	
Dextrose	60 mg
Xanthan gum (Rhodigel ultra fine)	15 mg
Thaumatin (Flavor enhancer)	5 to 10 ppm

Thoroughly blend the powder, reconstitute all of the powder with 5 ml to 20 ml distilled water and administer the suspension enterally to the patient.

Formulation 20: Unflavored Omeprazole Powder (single dose)	
Omeprazole powder USP	20 mg or 40 mg
Sodium bicarbonate USP	1500 mg
Parietal cell activator:	
Calcium chloride	200 mg
Other ingredients:	
Dextrose	60 mg
Xanthan gum (Rhodigel ulta fine)	15 mg
Thaumatin (Flavor enhancer)	5 to 10 ppm

Thoroughly blend the powder. Reconstitute all of the powder with 5 mL to 20 mL distilled water and administer the suspension enterally to the patient.

Formulation 21: Flavored Omeprazole Powder (single dose)	
Omeprazole powder USP	20 mg
Dibasic sodium Phosphate duohydrate	2000 mg
Sodium bicarbonate USP	840 mg to 1680 mg
Sucrose	2.6 g
Maltodextrin	200 mg
Cocoa processed with alkali*	180 mg
Corn syrup solids	600 mg
Xanthan gum	15 mg
Aspartame	15 mg
Thaumatin	2 mg
Soy lecithin	10 mg

*Parietal cell activator

Thoroughly blend the powder. Reconstitute all of the powder with 10 mL to 20 mL distilled water at the time of use.

Formulation 22: Unflavored Lansoprazole Powder (single dose)	
Lansoprazole powder USP	15 mg or 30 mg
Sodium bicarbonate USP	400 mg to 1500 mg

Optionally: Tribasic sodium phosphate to adjust pH for longer stability and enhanced buffering capacity (alternatively other Essential Buffers may be employed)

Thoroughly blend the powder. Reconstitute all of the powder with 5 mL to 20 mL distilled water at the time of use.

Formulation 23: Flavored Lansoprazole Powder (single dose)	
PPI:	
Lansoprazole powder USP	30 mg
Primary Essential Buffer(s):	
Dibasic Sodium Phosphate USP or Sodium bicarbonate USP	1500 mg
Sucrose	26 g
Maltodextrin	2 g
Cocoa processed with alkali*	18 mg
Corn syrup solids	600 mg
Soy lecithin	80 mg

*Parietal cell activator

Thoroughly blend the powder. Reconstitute all of the powder with 5 mL to 20 mL distilled water at the time of use.

Formulation 24: Unflavored Rabeprazole Powder (single dose)	
PPI:	
Rabeprazole sodium powder USP	20 mg
Primary Essential Buffer(s):	
Disodium phosphate duohydrate USP	2000 mg
Optional Secondary Essential Buffer(s)	
Tribasic sodium phosphate	100 mg

Thoroughly blend the powder and reconstitute with distilled water prior to administration. Optionally, thickeners and flavoring agents may be added as stated throughout this application. The anticipated volume for this powder would be 20 mL per dose. This formulation is designed to enhance stability of rabeprazole through the use of the common ion effect whereby sodium causes a "salting out" of rabeprazole sodium. This causes the rabeprazole sodium to remain insoluble thereby increasing its stability.

Formulation 25: Unflavored Rabeprazole Powder (single dose)	
PPI:	
Rabeprazole sodium powder USP	20 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	1200 mg
Secondary Essential Buffer(s):	
Trisodium phosphate USP	300 mg
Optional Secondary Essential Buffer(s):	
Sodium hydroxide or Tribasic potassium may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.	

Thoroughly blend the powder and reconstitute with 15 mL distilled water at the time of use.

Alternatively, a two part product may be employed comprising one part of about 5 to about 15 mL distilled water with a low concentration of Secondary Essential Buffer (e.g. trisodium phosphate (100 mg) or sodium hydroxide (50 mg)) used to dissolve an enteric-coated tablet of rabeprazole thereby producing a stable solution/suspension. This highly alkaline suspension containing low neutralization capacity and rabeprazole sodium may then be added with a second part containing the Primary Essential Buffer(s) having significant neutralization capacity. If desired other Secondary Essential Buffer(s) may be included with the Primary Essential Buffers. This formulation is designed to enable the use of the commercially available enteric-coated tablet of rabeprazole as the source of the PPI. This tablet requires disintegration prior to use as a liquid formulation. Part 1 (the low concentration of Secondary Essential Buffer) produces rapid dissolution of the delayed-release tablet as well as

prolonged stability of rabeprazole sodium in the liquid form. This enables the preparation to be prepared prior to administration and simply added to the Primary Essential Buffer(s) (part 2) prior to use.

Formulation 26: Unflavored Rabeprazole Powder (single dose)	
PPI:	
Rabeprazole sodium powder USP	20 mg
Primary Essential Buffer(s):	
Calcium lactate USP	700 mg
Calcium glycerophosphate	700 mg
Secondary Essential Buffer(s):	
Calcium hydroxide USP	15 mg

(Other Secondary Essential Buffers with cations of sodium or potassium may be added in higher or lower amounts to adjust pH for desirable stability.)

Thoroughly blend the powder. Reconstitute the powder with a liquid part comprising 10 mL glycerol and 10 mL distilled water at the time of use. Alternatively, the liquid for reconstitution may be only water (e.g. distilled) and contain some of the buffer. The liquid for reconstitution may be supplied as a buffered product (to pH 9–11) for dissolving rabeprazole sodium delayed-release tablets (if used as a source of rabeprazole sodium).

Formulation 27: Unflavored Esomeprazole Powder (single dose)	
PPI:	
Esomeprazole magnesium powder USP	20 mg
Primary Essential Buffer(s):	
Calcium lactate USP	800 mg
Calcium glycerophosphate	800 mg
Secondary Essential Buffer(s):	
Calcium hydroxide USP	15 mg

(Other Secondary Essential Buffers with cations of calcium or magnesium may be added in higher or lower amounts to adjust pH for desirable stability.)

Thoroughly blend the powder. Reconstitute the powder with a liquid part comprising of 10 mL distilled water at the time of use. The liquid for reconstitution may be supplied as a buffered product (to pH 8–11) for dissolving esomeprazole magnesium delayed release granules (if used as a source of esomeprazole magnesium).

Formulation 28: Omeprazole Two Part Tablet Two part tablets contain an outer buffer phase and inner buffer/PPI core. Enough for 6 tablets is weighed out.	
Inner Core:	
PPI:	
Omeprazole powder USP (or esomeprazole magnesium or omeprazole sodium).	120 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	1200 mg

-continued

Formulation 28: Omeprazole Two Part Tablet Two part tablets contain an outer buffer phase and inner buffer/PPI core. Enough for 6 tablets is weighed out.	
Outer Phase:	
Sodium bicarbonate USP	3960 mg

(Secondary Essential Buffers such as trisodium phosphate, tripotassium phosphate or sodium carbonate or others may be added to enhance neutralization capacity.)

Thoroughly blend the powders for the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of ⅜" diameter. The powder mixture is then formulated into small tablets by conventional pharmaceutical procedures. Repeat for five additional tablets, then set these small inner tablets aside.

The outside layer surrounding the PPI tablet serves as a pH-buffering zone. Enough sodium bicarbonate for 6 tablets is weighed out with approximately 280 mg per tablet for a total of 1680 mg sodium bicarbonate USP. Then weigh out approximately 280 mg of the resultant blend and add to a die of ½" diameter. Press through a full motion to compact the powder into a tablet. Place the tablet back into the ½ inch die and then place the smaller ⅜" tablet (inner tablet) on top of the ½" tablet and center it. Add approximately 380 mg sodium bicarbonate to the die on top of the ½" tablet and the ⅜" tablet. Press through a full motion to compact the materials into one tablet. The approximate weight of each tablet is 815 mg to 890 mg containing 20 mg omeprazole. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch may be added. The outer layer may also comprise pharmaceutically acceptable tablet exipients. Optional coatings can also be employed, for example, light film coatings and coatings to repel ultraviolet light as is known in the art.

Magnesium oxide or magnesium hydroxide may be substituted for the sodium bicarbonate outer phase. Enough magnesium oxide for 6 tablets is weighed out with approximately 280 mg per tablet for a total of 1680 mg magnesium oxide USP. Then weigh out approximately 280 mg of the resultant blend and add to a die of ½" diameter. Press through a full motion to compact the powder into a tablet. Place the tablet back into the ½ inch die and then place the smaller ⅜" tablet (inner tablet) on top of the ½" tablet and center it. Add approximately 380 mg magnesium oxide to the die on top of the ½" tablet and the ⅜" tablet. Press through a full motion to compact the materials into one tablet. The approximate weight of each tablet is 815 mg to 890 mg containing 20 mg omeprazole. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch, croscarmelose sodium or microcrystalline cellulose (MCC) and colloidal silicone dioxide (CSD) may be added. The outer layer may also comprise pharmaceutically acceptable tablet exipients. Optional coatings can also be employed, for example, light film coatings and coatings to repel ultraviolet light as is known in the art.

The outer phase can alternatively comprise a combination of sodium bicarbonate and magnesium oxide.

Formulation 29: Lansoprazole Two Part Tablet
Enough for 6 tablets is weighed out.

Inner Core:	
PPI:	
Lansoprazole powder USP	180 mg
Primary Essential Buffer:	
Sodium bicarbonate USP	1200 mg
Outer Phase:	
Sodium bicarbonate USP	3960 mg

Thoroughly blend the powders of the inner core, then weigh out approximately 230 mg of the resultant blend and add to a die of 3/8" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 825 mg to 900 mg. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch may be added.

Formulation 30: Pantoprazole Two Part Tablet
Enough for 6 tablets is weighed out.

Inner Core:	
PPI:	
Pantoprazole powder USP (or pantoprazole sodium)	240 mg
Primary Essential Buffer:	
Sodium bicarbonate USP	1200 mg
Outer Phase:	
Sodium bicarbonate USP	3960 mg

Thoroughly blend the powders for the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of 3/8" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 835 mg to 910 mg. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch or croscarmelose sodium may be added.

Formulation 31: Omeprazole or esomeprazole two part tablet.
Enough for 6 tablets is weighed out.

Inner Core:	
PPI:	
Omeprazole powder USP (or esomeprazole or omeprazole sodium).	120 mg
Primary Essential Buffer:	
Sodium bicarbonate	1200 mg
Outer Phase:	
Sodium bicarbonate	3960 mg

Thoroughly blend the powders of the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of 3/8" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 815 mg to 890 mg. Binders such as tapioca or PVP and disintigrants have been mentioned and may be added. Secondary Essential Buffers such as trisodium phosphate, tripotassium phosphate or sodium carbonate or others may be added to enhance neutralization capacity.

Formulation 32: Lansoprazole Two part tablet
Enough for 6 tablets is weighed out.

Inner Core:	
PPI:	
Lansoprazole powder USP	180 mg
Primary Essential Buffer:	
Sodium bicarbonate	1200 mg
Outer Phase:	
Sodium bicarbonate	3960 mg

Thoroughly blend the powder of the inner core, then weigh out approximately 230 mg of the resultant blend and add to a die of 3/8" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 825 mg to 900 mg. Binders such as tapioca or PVP and disintigrants have been mentioned and may be added. Secondary Essential Buffers such as trisodium phosphate, tripotassium phosphate or sodium carbonate or others may be added to enhance neutralization capacity.

Formulation 33: Pantoprazole Two part tablet
Enough for 6 tablets is weighed out.

Inner Core:	
PPI:	
Pantoprazole sodium powder USP	240 mg
Primary Essential Buffer:	
Sodium bicarbonate	1200 mg
Outer Phase:	
Sodium bicarbonate	3960 mg

Thoroughly blend the powders of the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of 3/8" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 835 mg to 910 mg. Binders such as tapioca or PVP and disintegrants may also be added. Secondary Essential Buffers, such as trisodium phosphate,

tripotassium phosphate, sodium carb[redacted]r others, may be added to enhance neutralization capacity.

Formulation 34: Omeprazole 20 mg Two-Part Tablet	
Inner Core:	
PPI:	
Omeprazole enteric coated granules (base, or sodium salt or esomeprazole sodium or magnesium)	20 mg
Outer Phase:	
Sodium bicarbonate powder USP	1000 mg

The inner core is created as is known in the art such that the enteric coatings on the granules remain substantially intact. The outer phase is bound to the inner core as described in Formulation 28. Other variations of this tablet include a uniform enteric coating surrounding the PPI of the inner core instead of separate enteric coated granules.

Formulation 35: Lansoprazole 30 mg Two-Part Tablet	
Inner Core:	
PPI:	
Lansoprazole enteric coated granules	30 mg
Outer Phase:	
Sodium bicarbonate powder USP	1000 mg

This two-part tablet is formulated as per Formulation 34.

Formulation 36: Rabeprazole 20 mg Two-Part Tablet	
Inner Core:	
PPI:	
Rabeprazole enteric coated granules	20 mg

-co[redacted]ued

Formulation 36: Rabeprazole 20 mg Two-Part Tablet	
Outer Phase:	
Sodium bicarbonate powder USP	1000 mg

This two-part tablet is formulated as per Formulation 34.

Formulation 37: Omeprazole Two Part Tablet Enough for 6 tablets is weighed out	
Inner Core:	
Omeprazole	120 mg
Sodium bicarbonate power USP	1200 mg
Outer Phase:	
Magnesium oxide	1500 mg
Optional-calcium carbonate	3000 mg

The omeprazole and sodium bicarbonate of the inner core are homogeneously mixed and formed as in Formulation 28. The outer phase is combined with the inner core as in Formulation 28.

Formulation 38: Combination Antacid and Enteric Coated Dosage Form	
Omeprazole enteric coated granules or enteric coated tablet	20 mg (or an equivalent dose of another PPI)
Calcium carbonate	1000 mg

The above components are combined with care exerted to ensure that the enteric coating is not crushed or otherwise compromised. The resulting combination is then formed into compressed tablets or placed in capsules as is known in the pharmaceutical art. If enteric coated granules are employed, they are generally, but not required, dispersed throughout the tablet or capsule. If an enteric coated tablet is alternatively utilized, it forms a central core, which is uniformly surrounded by the calcium carbonate in either a compressed tablet or in a larger capsule. In another embodiment, a capsule containing enteric coated granules of PPI can be placed within a larger capsule containing the calcium carbonate.

It should be noted that other buffering agents can be utilized in lieu of or in combination with calcium carbonate. The buffer(s) employed is present in an amount of at least about 5 mEq per dose of the composition with the preferred range been 7.5 to 15 mEq. For example, sodium bicarbonate may be preferred over calcium carbonate and other antacids (such as magnesium or aluminum salts) because in many cases, sodium bicarbonate more quickly lowers gastric pH.

Formulation 39: Combination Rapid Release and Delayed Released PPI and Antacid	
Inner core:	10 or 20 mg (or an equivalent dose of another
Omeprazole enteric coated granules or enteric coated tablet	PPI)

-continued

Formulation 39: Combination Rapid Release and Delayed Released PPI and Antacid	
Outer phase:	
Omeprazole powder	10 or 20 mg (or equivalent dose of another PPI)
Calcium Carbonate powder	1000 mg

The constituents of the outer phase are uniformly mixed. The inner core is created as is known in the art such that the enteric coatings on the granules or tablet remain substantially intact. The outer phase is bound to the inner core as described herein and as known in the art.

Formulation 40: Soft Chewable PPI-Buffer Dosage Form

Omeprazole 10 or 20 mg (or an equivalent dose of another PPI) is combined with the ingredients of a soft chewable antacid tablet (e.g., Viactiv®), which comprises calcium carbonate 500 or 1000 mg, corn syrup, sugar, chocolate non fat milk, cocoa butter, salt, soy lecithin, glyceryl monostearate, flavoring (e.g., caramel), carrageenan, and sodium phosphate. Vitamins D3 and/or K1 can also be added. The finished chew tablets are administered to patients once to thrice daily for gastric acid related disorders.

For all formulations herein, multiple doses may be proportionally compounded as is known in the art.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation. All patents and other references cited herein are incorporated herein by reference in their entirety. Obviously, many modifications, equivalents, and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described.

I claim:

1. A solid oral pharmaceutical dosage form that is not enteric-coated, comprising:

active ingredients consisting essentially of:

(a) at least one proton pump inhibitor (PPI) selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, and an enantiomer, isomer, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and

(b) at least one Primary Essential Buffer and at least one optional Secondary Essential Buffer in a total amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor; and

a pharmaceutically-acceptable excipient;

wherein the dosage form is selected from the group consisting of a suspension tablet, chewable tablet, two-part tablet, effervescent powder, and effervescent tablet.

2. The dosage form of claim 1, wherein the proton pump inhibitor is in an amount from approximately 10 mg to approximately 100 mg.

3. The dosage form of claim 1, wherein the proton pump inhibitor is omeprazole.

4. The dosage form of claim 1, wherein the proton pump inhibitor is lansoprazole.

5. The dosage form of claim 1, wherein the proton pump inhibitor is pantoprazole.

6. The dosage form of claim 1, wherein the proton pump inhibitor is rabeprazole.

7. The dosage form of claim 1, wherein the proton pump inhibitor is esomeprazole.

8. The dosage form of claim 1, wherein the proton pump inhibitor is pariprazole.

9. The dosage form of claim 1, wherein the proton pump inhibitor is leminoprazole.

10. The dosage form of claim 1, wherein the Primary Essential Buffer is selected from the group consisting of sodium bicarbonate, sodium sesquicarbonate, dibasic sodium phosphate, sodium tripolyphosphate, tetrasodium pyrophosphate, sodium citrate, calcium citrate, calcium carbonate, magnesium oxide, sodium gluconate, sodium lactate, sodium acetate, dipotassium phosphate, tetrapotassium pyrophosphate, potassium bicarbonate, calcium lactate, calcium glycerophosphate, calcium gluconate, magnesium lactate, magnesium gluconate, and magnesium hydroxide, and mixtures thereof.

11. The dosage form of claim 10, wherein the Primary Essential Buffer is sodium bicarbonate.

12. The dosage form of claim 11, wherein the sodium bicarbonate is in an amount from about 400 mg to about 4000 mg.

13. The dosage form of claim 11, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

14. The dosage form of claim 10, wherein the Primary Essential Buffer is calcium carbonate.

15. The dosage form of claim 14, wherein the calcium carbonate is in an amount from about 400 mg to about 4000 mg.

16. The dosage form of claim 14, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

17. The dosage form of claim 14, wherein the calcium carbonate is in an amount of at least about 700 mg.

18. The dosage form of claim 1, wherein the Secondary Essential Buffer is selected from the group consisting essentially of sodium carbonate, potassium carbonate, trisodium phosphate, tripotassium phosphate, calcium hydroxide, and sodium hydroxide.

19. The dosage form of claim 1, wherein the pharmaceutically-acceptable excipient comprises at least one flavoring agent.

20. The dosage form of claim 19, wherein the flavoring agent compnses apple, caramel, meat, chocolate, root beer, maple, cherry, coffee, mint, licorice, nut, butter, butterscotch, peanut butter, aspartame, chocolate, thalmantin, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

21. The dosage form of claim 1, wherein the pharmaceutically-acceptable excipient comprises an anti-foaming agent.

22. The dosage form of claim 1, wherein the pharmaceutically-acceptable excipient comprises a binder,

diluent, lubricant, disintegrant, colorant, antioxidant, chelating agent, anti-caking agent, moistening agent, preservative, or coating.

23. The dosage form of claim **10**, wherein the Primary Essential Buffer is sodium bicarbonate and calcium carbonate.

24. A solid oral pharmaceutical dosage form that is not enteric-coated, comprising: an outer layer and an inner core;

the outer layer comprising active ingredients consisting essentially of at least one Primary Essential Buffer; and

the inner core comprising active ingredients consisting essentially of at least one proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base, or salt thereof, and at least one buffering agent selected from the group consisting of a Primary Essential Buffer and a Secondary Essential Buffer;

wherein the total amount of the proton pump inhibitor is approximately 5 mg to approximately 300 mg; and the total amount of the buffering agent is approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor.

25. A method of administering the dosage form of claim **1**, comprising: orally administering the dosage form to a subject, wherein the amount of the Primary Essential Buffer and the optional Secondary Essential Buffer is effective to elevate pH of gastric fluid of the subject upon oral administration to at least 3.7 from time the proton pump inhibitor comes in contact with the gastric fluid throughout dwell time in the stomach.

26. The method of claim **25**, wherein the amount of the Primary Essential Buffer and the optional Secondary Essential Buffer is effective to elevate the pH of the gastric fluid of the subject upon oral administration to at least 4.6.

27. The method of claim 25, wherein the amount of the Primary Essential Buffer and the optional Secondary Essential Buffer is effective to elevate the pH of the gastric fluid of the subject upon oral administration to at least 4.8.

28. The method of claim **25**, wherein the amount of the Primary Essential Buffer and the optional Secondary Essential Buffer is effective to elevate the pH of the gastric fluid of the subject upon oral administration to at least 5.6.

29. A non-enteric coated solid oral pharmaceutical dosage form, comprising:

(a) active ingredients consisting essentially of:

(i) a proton pump inhibitor (PPI) selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, and an enantiomer, isomer, free base, and salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and

(ii) at least one Primary Essential Buffer and at least one optional Secondary Essential Buffer in a total amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor; and

(b) a pharmaceutically-acceptable excipient;

wherein the dosage form is created by a method comprising:

i) blending the proton pump inhibitor, the Primary Essential Buffer, the optional Secondary Essential Buffer, and the pharmaceutically-acceptable excipient; and

ii) formulating the proton pump inhibitor, the Primary Essential Buffer, the optional Secondary Essential Buffer, and the pharmaceutically-acceptable excipient into a powder, tablet, suspension tablet, chewable tablet, capsule, two-part tablet, two-part capsule, effervescent powder, pellet, granule or effervescent tablet.

* * * * *

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Phillips

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(45) **Date of Patent: *Mar. 2, 2004**

(54) **SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHODS OF USING SAME**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(63) Continuation-in-part of application No. 09/901,942, filed on Jul. 9, 2001, which is a continuation-in-part of application No. 09/481,207, filed on Jan. 11, 2000, now Pat. No. 6,489,346, which is a continuation-in-part of application No. 09/183,422, filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of application No. 08/680,376, filed on Jul. 15, 1996, now Pat. No. 5,840,737.

(60) Provisional application No. 60/009,608, filed on Jan. 4, 1996.

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(52) **U.S. Cl.** **514/338**; 514/395; 424/717
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(57) **ABSTRACT**

Disclosed herein are methods, kits, combinations, and compositions for treating gastric acid disorders employing pharmaceutical compositions comprising a proton pump inhibiting agent (PPI) and a buffering agent in a pharmaceutically acceptable carrier.

51 Claims, 7 Drawing Sheets

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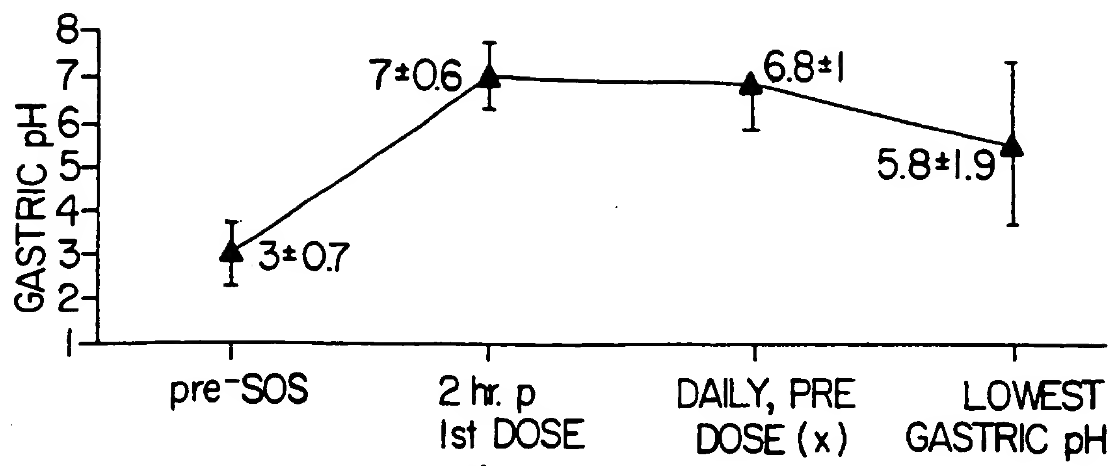
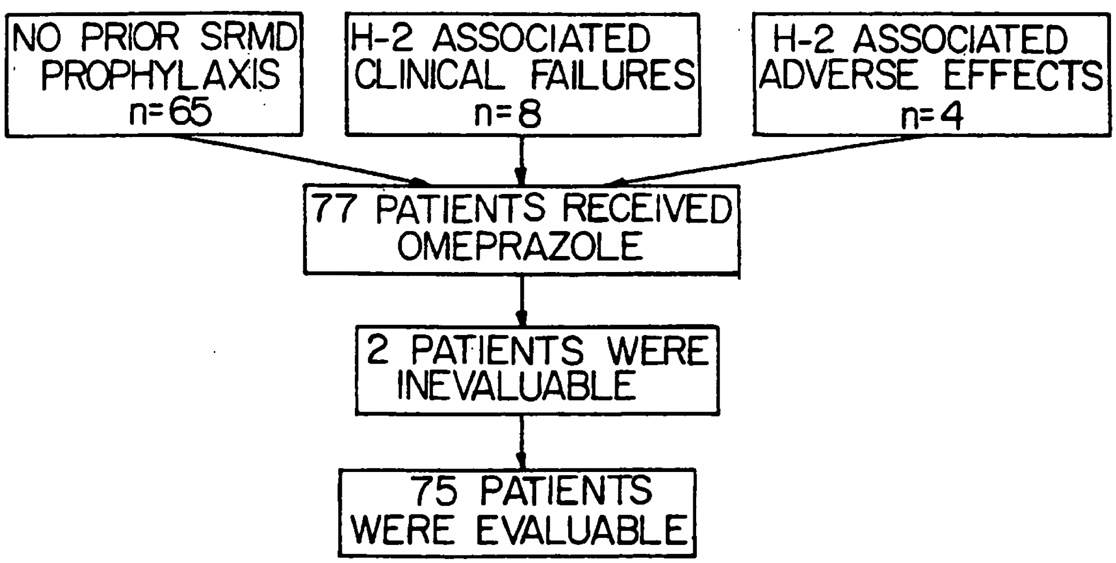


Fig. 1



OVERALL PATIENT ENROLLMENT SCHEME

Fig. 2

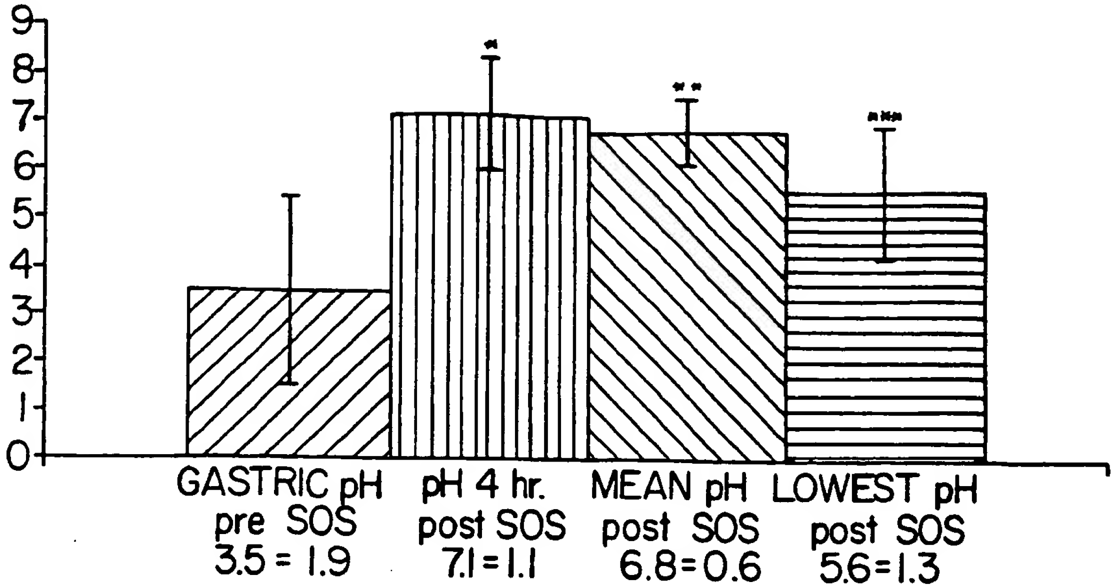

9
8
7
6
5
4
3
2
1
0
*
**
***
GASTRIC pH pre SOS 3.5 = 1.9
pH 4 hr. post SOS 7.1 = 1.1
MEAN pH post SOS 6.8 = 0.6
LOWEST pH post SOS 5.6 = 1.3

Fig. 3

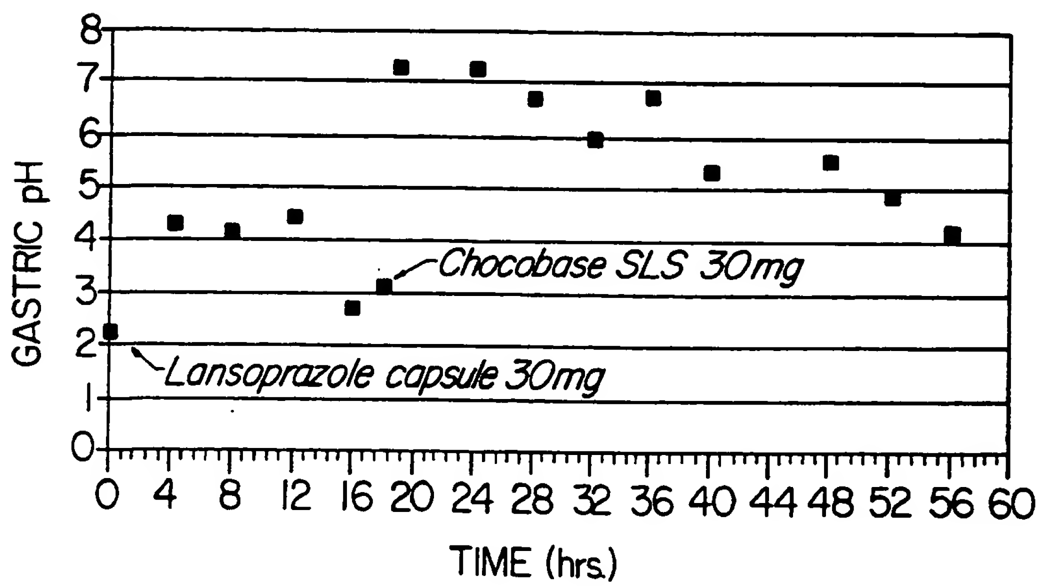

GASTRIC pH
8
7
6
5
4
3
2
1
0
Chocobase SLS 30mg
Lansoprazole capsule 30mg
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
TIME (hrs.)

Fig. 4

Graph 1

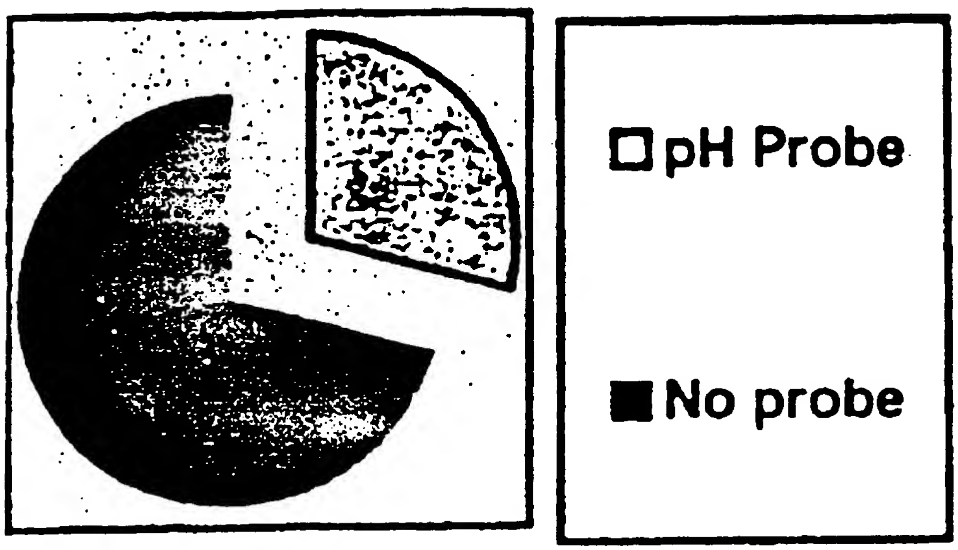


FIGURE 5

Graph 2

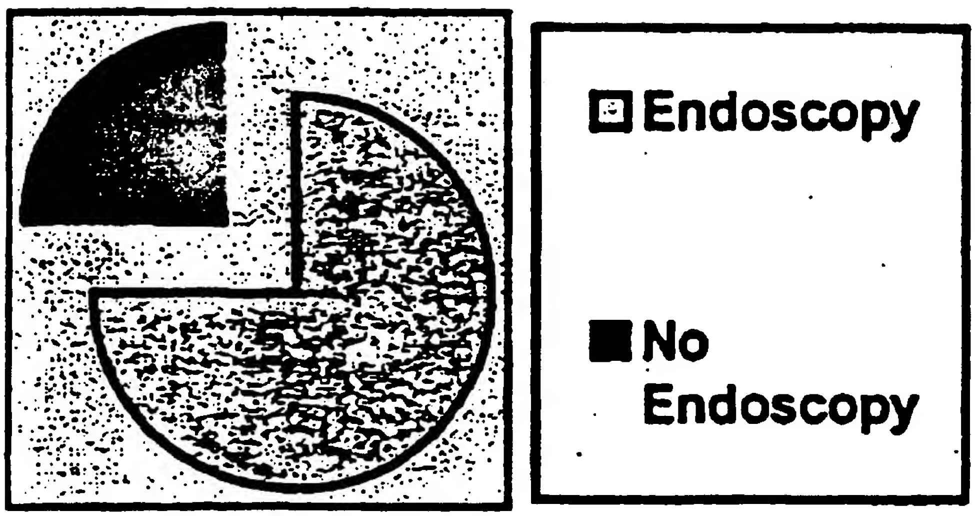


FIGURE 6

Graph 3

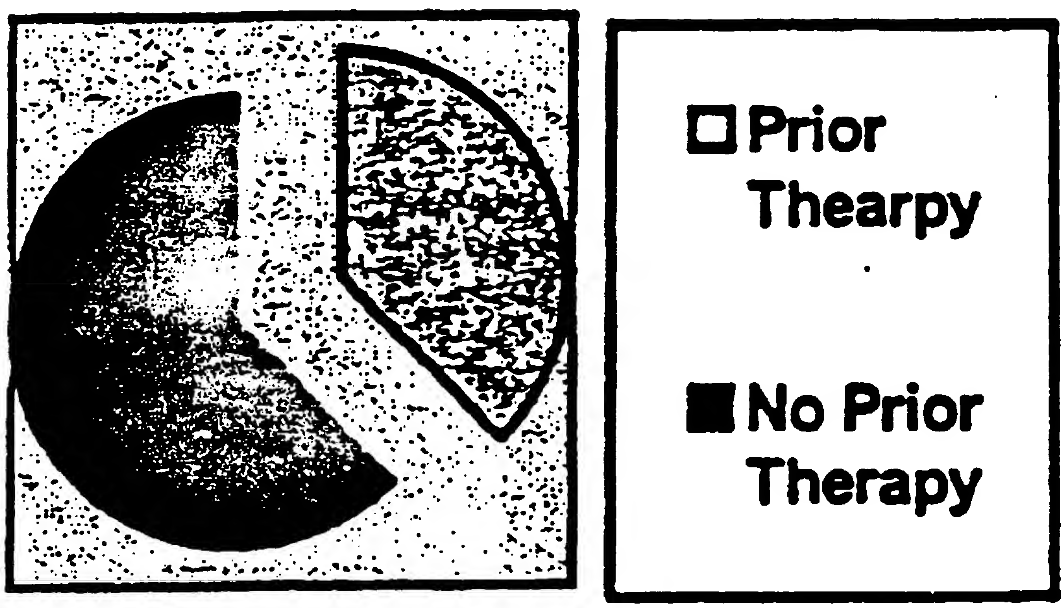


FIGURE 7

Graph 4

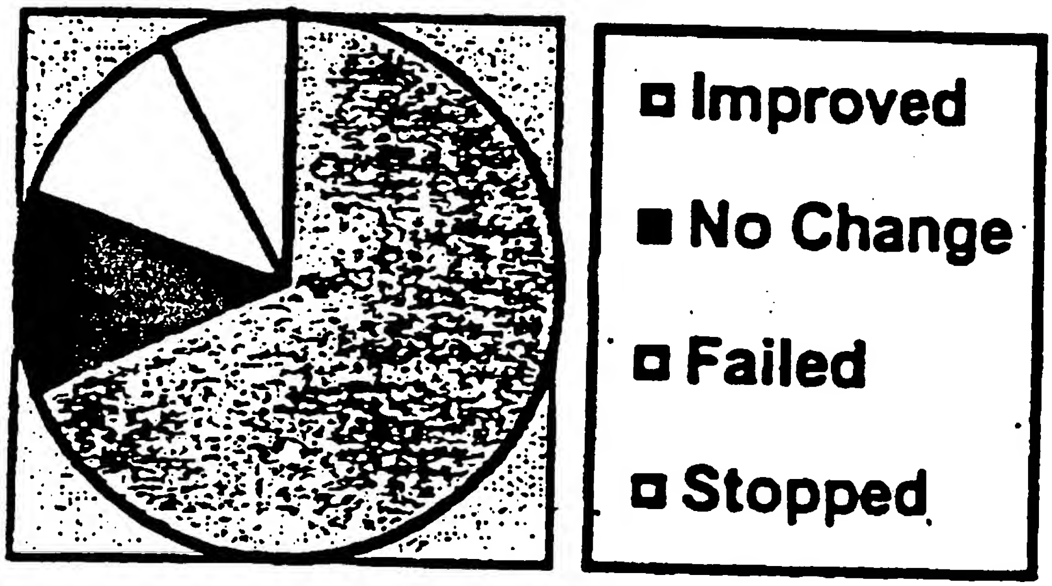
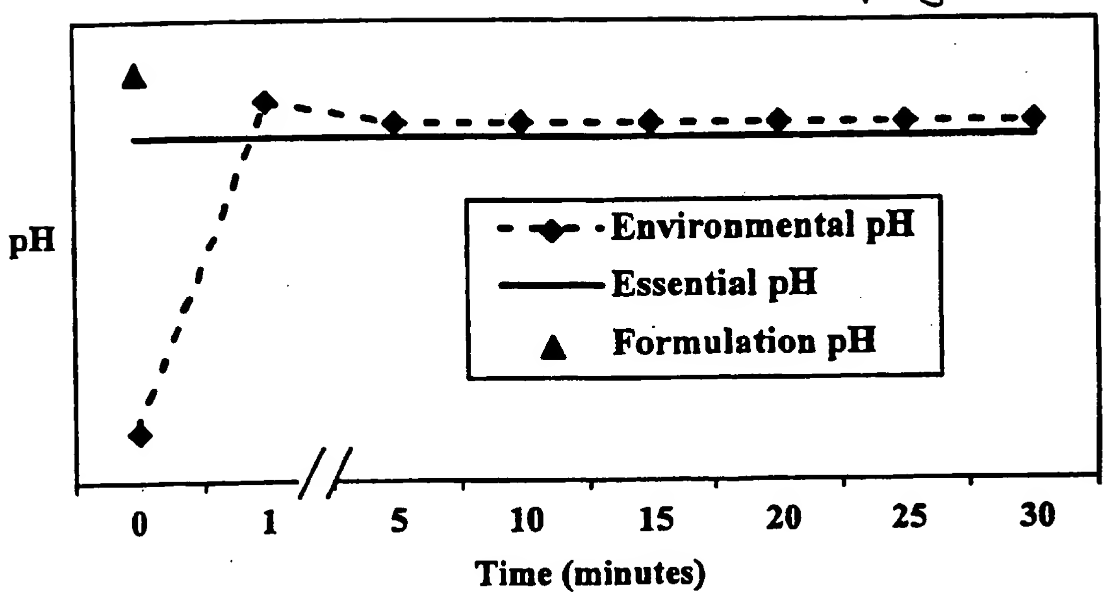


FIGURE 8

Fig. 9


pH
Environmental pH
Essential pH
Formulation pH
0
1
5
10
15
20
25
30
Time (minutes)

SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHODS OF USING SAME

This application is a continuation-in-part of U.S. patent application Ser. No. 09/901,942, filed on Jul. 9, 2001, which is a continuation-in-part of U.S. patent application Ser. No. 09/481,207, filed on Jan. 11, 2000, now U.S. Pat. No. 6,489,346, which is a continuation-in-part of U.S. patent application Ser. No. 09/183,422, filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/680,376, filed on Jul. 15, 1996, now U.S. Pat. No. 5,840,737, which claims priority to U.S. Provisional Application Serial No. 60/009,608, filed on Jan. 4, 1996. This application claims priority to all such previous applications, and such applications are hereby incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to pharmaceutical preparations comprising substituted benzimidazole proton pump inhibiting agents.

BACKGROUND OF THE INVENTION

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole, that inhibits gastric acid secretion. Omeprazole belongs to a class of anti secretory compounds called proton pump inhibitors proton pump inhibiting agents ("PPIs") that do not exhibit aniti-cholinergic or H_2 histamine antagonist properties. Drags of this class suppress gastric acid secretion by the specific inhibition of the H^+, K^+-ATPase enzyme system (proton pump) at the secretory surface of the gastric parietal cell.

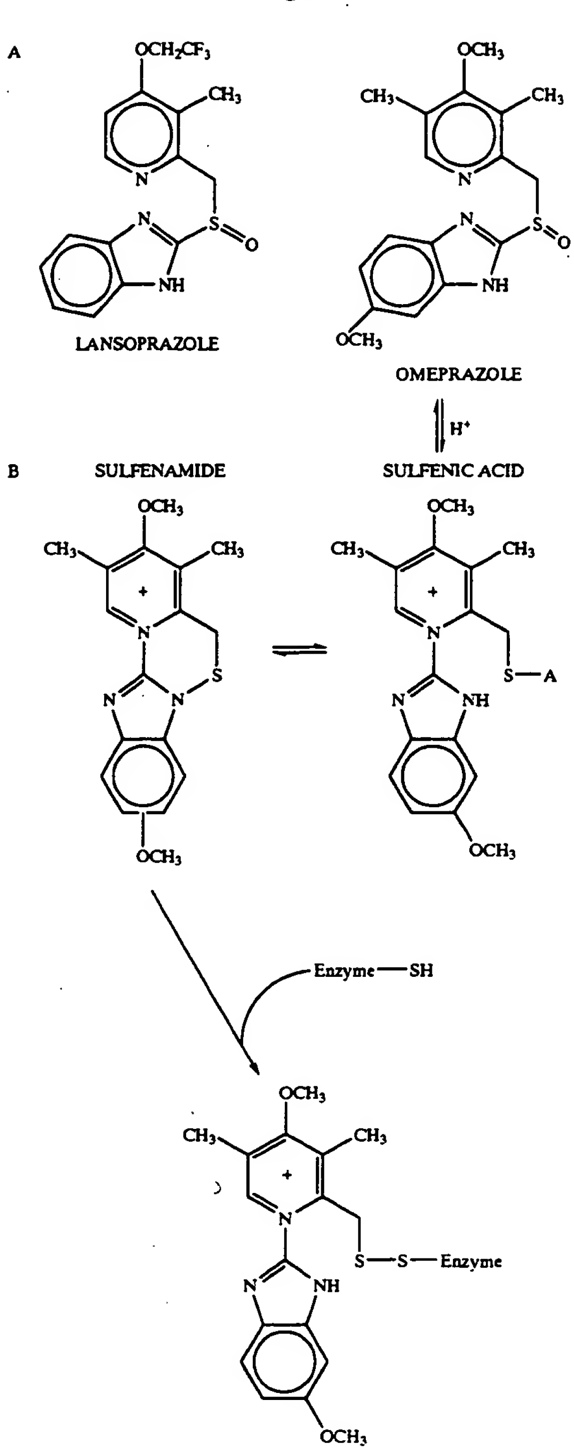
Typically, omeprazole, lansoprazole and other proton pump inhibitors are formulated in an enteric-coated solid dosage form (as either a delayed-release capsule or tablet) or as an intravenous solution (as a product for reconstitution), and are prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. These above-listed conditions commonly arise in healthy or critically ill patients, and may be accompanied by significant upper gastrointestinal bleeding.

H_2-antagonists, antacids, and sucralfate are commonly administered to minimize the pain and the complications related to these conditions. These drugs have certain disadvantages associated with their use. Some of these drugs are not completely effective in the treatment of the aforementioned conditions and/or produce adverse side effects, such as mental confision, constipation, diarrhea, and thrombocytopenia. H_2-antagonists, such as ranitidine and cimetidine, are relatively costly modes of therapy, particularly in NPO patients, which frequently require the use of automated infusion pumps for continuous intravenous infusion of the drug.

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, *Pathogenesis, Diagnosis and Treatment of Acute Gastric Mucosa Lesions,* CLIN GASTROENTEROL 13:635–650 (1984)). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., *The Prevention of Gastrointestinal Tract Bleeding in Patients in an Intensive Care Unit,* SURG. GYNECOL. OBSTET., 153:214–220 (1981); Larson et al., *Gastric Response to Severe Head Injury,* AM. J. SURG. 147:97–105 (1984); Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291:925–929 (1974); Skillman et al., *Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated with Lethal Hemorrhage From Acute Stress Ulceration,* AM. J. SURG., 117:523–530 (1969); and Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377–381 (1994)). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377–381 (1994)). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., *Continuous Intravenous cimetidine Decreases Stress-related Upper Gastro-intestinal Hemorrhage Without Promoting Pneumonia,* CRIT. CARE MED., 21:19–39 (1993)). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291:925–929 (1974); Peura and Johnson, *Cimetidine for Prevention and Treatment of Gastroduodenal Mucosal Lesions in Patients in an Intensive Care Unit,* ANN INTERN MED., 103:173–177 (1985)). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.

Omeprazole (Prilosec(®), lansoprazole (Prevacid®) and other proton pump inhibitors reduce gastric acid production by inhibiting H^{30}, K^+-ATPase of the parietal cell—the final common pathway for gastric acid secretion (Fellenius et al., *Substituted Benzimidazoles Inhibit Gastric Acid Secretion by Blocking H^+, K^+-ATPase,* NATURE, 290:159–161 (1981); Wallmark et al, *The Relationship Between Gastric Acid Secretion and Gastric H^+, K^+-ATPase Activity,* J. BIOL.CHEM., 260:13681–13684 (1985); Fryklund et al., *Function and Structure of Parietal Cells After H^+, K^+-ATPase Blockade,* AM. J. PHYSIOL., 254 (3 PT 1); G399–407 (1988)).

Proton pump inhibitors contain a sulfinyl group in a bridge between substituted benzimidazole and pyridine rings, as illustrated below.



ENZYME-INHIBITOR COMPLEX

At neutral pH, omeprazole, lansoprazole and other proton pump inhibitors are chemically stable, lipid-soluble, weak bases that are devoid of inhibitory activity. These neutral weak bases reach parietal cells from the blood and diffuse into the secretory canaliculi, where the drugs become protonated and thereby trapped. The protonated agent rearranges to form a sulfenic acid and a sulfenamide. The sulfenamide interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane-spanning H^+, K^+-ATPase (Hardman et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, p. 907 (9^{th} ed. 1996)). Omeprazole and lansoprazole, therefore, are prodrugs that must be activated to be effective. The specificity of the effects of proton pump inhibitors is also dependent upon: (a) the selective distribution of H^+, K^+-ATPase; (b) the requirement for acidic conditions to catalyze generation of the reactive inhibitor; and (c) the trapping of the protonated drug and the cationic sulfenamide within the acidic canaliculi and adjacent to the target enzyme. (Hardman et al., 1996).

Omeprazole and lansoprazole are available for oral administration as enteric-coated granules in gelatin capsules. Other proton pump inhibitors such as rabeprazole and pantoprazole are supplied as enteric-coated dosage forms. The enteric dosage forms of the prior art have been employed because they are acid labile; thus, it is important that these drugs not be exposed to low pH gastric acid prior to absorption. Although these drugs are stable at alkaline pH, they are destroyed rapidly as pH falls (e.g., by gastric acid). Therefore, if the micro-encapsulation or the enteric coating is disrupted (e.g., trituration to compound a liquid, or chewing the capsule), the dosage forms of the prior art will be exposed to degradation by the gastric acid in the stomach.

The absence of an intravenous or oral liquid dosage form in the United States has limited the testing and use of omeprazole, lansoprazole and rabeprazole in the critical care patient population. Barie et al., *Therapeutic Use of Omeprazole for Refractory Stress-induced Gastric Mucosal Hemorrhage*, CRIT. CARE MED., 20:899–901 (1992) have described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multi-organ failure. However, such pellets are not ideal as they can aggregate and occlude such tubes, and they are not suitable for patients who cannot swallow the pellets. AM J. HEALTH-SYST PHARM 56:2327–30 (1999).

Proton pump inhibitors such as omeprazole represent an advantageous alternative to the use of H_2-antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage. However, in their current form (capsules containing enteric-coated granules or enteric-coated tablets), proton pump inhibitors can be difficult or impossible to administer to patients who are either unwilling or unable to swallow tablets or capsules, such as critically ill patients, children, the elderly, and patients suffering from dysphagia. Therefore, it would be desirable to formulate a proton pump inhibitor solution or suspension which can be enterally delivered to a patient thereby providing the benefits of the proton pump inhibitor without the drawbacks of the current enteric-coated solid dosage forms.

Omeprazole, the first proton pump inhibitor introduced into use, has been formulated in many different embodiments such as in a mixture of polyethylene glycols, adeps solidus and sodium lauryl sulfate in a soluble, basic amino acid to yield a formulation designed for administration in the rectum as taught by U.S. Pat. No. 5,219,870 to Kim.

U.S. Pat. No. 5,395,323 to Berglund ('323) discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient. The '323 patent teaches the use of an omeprazole tablet which is placed in the device and dissolved by normal saline, and infused parenterally into the patient. This device and method of parenteral infusion of omeprazole does not provide the omeprazole solution as an enteral product, nor is this omeprazole solution directly administered to the diseased or affected areas, namely the

stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate antacid effect of the present formulation.

U.S. Pat. No. 4,786,505 to Lovgren et al. discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The core is then enterically coated. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH. The powder mixture is then formulated into enteric-coated small beads, pellets, tablets and may be loaded into capsules by conventional pharmaceutical procedures. This formulation of omeprazole does not teach a non-enteric-coated omeprazole dosage form which can be enterally administered to a patient who may be unable and/or unwilling to swallow capsules, tablets or pellets, nor does it teach a convenient form which can be used to make an omeprazole or other proton pump inhibitor solution or suspension.

Several buffered omeprazole oral solutions/suspensions have been disclosed. For example, Pilbrant et al., *Development of an Oral Formulation of Omeprazole,* SCAND. J. GASTROENT. 20(Suppl. 108): 113–120 (1985) teaches a suspension of micronized omeprazole, 60 mg, in 50 ml of water also containing 8 mmoles of sodium bicarbonate. The suspension was administered as follows: After fasting for at least 10 hours, patients were given a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later the patients took the omeprazole suspension and rinsed it down with another 50 ml of sodium bicarbonate solution. Ten (10), 20 and 30 minutes later, a further 50 ml of sodium bicarbonate solution was administered.

Andersson et el., *Pharmacokinetics of Various Single Intravenous and Oral Doses of Omeprazole,* EUR J. CLIN. PHARMACOL. 39:195–197 (1990) discloses 10 mg, 40 mg, and 90 mg of oral omeprazole dissolved in PEG 400, sodium bicarbonate and water. The concentration of omeprazole cannot be determined, as volumes of diluent are not disclosed. Nevertheless, it is apparent from this reference that multiple doses of sodium bicarbonate were administered with and after the omeprazole suspension.

Andersson et al., *Pharmacokinetics and Bioavailability of Omeprazole After Single and Repeated Oral Administration in Healthy Subjects,* BR. J. CLIN. PHARMAC. 29:557–63 (1990) teaches the oral use of 20 mg of omeprazole, which was dissolved in 20 g of PEG 400 (sp. gravity=1.14) and diluted with 50 ml of water containing 8 mmoles of sodium bicarbonate. In order to protect the omeprazole from gastric acid, the buffered solution was given with 48 mmoles of sodium bicarbonate in 300 ml of water.

Regardh et al., *The Pharmacokinetics of Omeprazole in Humans—A Study of Single Intravenous and Oral Doses,* THER. DRUG MON. 12:163–72 (1990) discloses an oral dose of omeprazole at a concentration 0.4 mg/ml after the drug was dissolved in PEG 400, water and sodium bicarbonate (8 mmoles). A solution containing 16 mmoles of sodium bicarbonate in 100 ml of water was concomitantly given with the omeprazole solution. That dose was followed by a solution of 50 ml of 0.16 mol/L sodium bicarbonate that was used for rinsing the vessel. In both the IV and oral experiment, 50 ml of 0.16 mol/L sodium bicarbonate was administered 5 minutes before administration, and 10, 20 and 30 minutes post-dose.

Landahl et al., *Pharmacokinetics Study of Omeprazole in Elderly Healthy Volunteers,* CLIN. PHARMACOKINETICS 23 (6): 469–476 (1992) teaches the use of an oral dose of 40 mg of omeprazole dissolved in PEG 400, sodium bicarbonate and water. This reference does not disclose the final concentrations utilized. Again, this reference teaches the multiple administration of sodium bicarbonate (8 mmol/L and 16 mmol/L) after the omeprazole solution.

Andersson et al., *Pharmacokinetics of [^{14}C] Omeprazole in Patients with Liver Cirrhosis,* CLIN. PHARMACOKINETICS 24(1): 71–78 (1993) discloses the oral administration of 40 mg of omeprazole, which was dissolved in PEG 400, water and sodium bicarbonate. This reference does not teach the final concentration of the omeprazole solution administered, although it emphasizes the need for pre, concomitant and post sodium bicarbonate dosing with a total of 48 mmoles to prevent acid degradation of the drug.

Nakagawa, et al., *Lansoprazole: Phase I Study of lansoprazole (AG-1749) Anti-ulcer Agent,* J. CLIN. THERAPEUTICS & MED.(1991) teaches the oral administration of 30 mg of lansoprazole suspended in 100 ml of sodium bicarbonate, which was administered to patients through a nasogastric tube.

All of the buffered omeprazole solutions described in these references were administered orally, and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration. In all of these studies, repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration. In the above-cited studies, as much as 48 mmoles of sodium bicarbonate in 300 ml of water must be ingested for a single dose of omeprazole to be orally administered.

The buffered omeprazole solutions of the above cited prior art require the ingestion of large amounts of sodium bicarbonate and large volumes of water by repeated administration. This has been considered necessary to prevent acid degradation of the omeprazole. In the above-cited studies, basically healthy volunteers, rather than sick patients, were given dilute buffered omeprazole utilizing pre-dosing and post-dosing with large volumes of sodium bicarbonate.

The administration of large amounts of sodium bicarbonate can produce at least six significant adverse effects, which can dramatically reduce the efficacy of the omeprazole in patients and reduce the overall health of the patients. First, the fluid volumes of these dosing protocols would not be suitable for sick or critically ill patients who must receive multiple doses of omeprazole. The large volumes would result in the distention of the stomach and increase the likelihood of complications in critically ill patients such as the aspiration of gastric contents.

Second, because bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their reflux disease as the belching can cause upward movement of stomach acid (Brunton, *Agents for the Control of Gastric Acidity and Treatment of Peptic Ulcers,* IN, Goodman AG, et al. *The Pharmacologic Basis of Therapeutics.* (New York, p. 907 (1990)).

Third, patients with conditions such as hypertension or heart failure are standardly advised to avoid the intake of excessive sodium as it can cause aggravation or exacerba-

tion of their hypertensive conditions (Brunton, supra). The ingestion of large amounts of sodium bicarbonate is inconsistent with this advice.

Fourth, patients with numerous conditions that typically accompany critical illness should avoid the intake of excessive sodium bicarbonate as it can cause metabolic alkalosis that can result in a serious worsening of the patient's condition.

Fifth, excessive antacid intake (such as sodium bicarbonate) can result in drug interactions that produce serious adverse effects. For example, by altering gastric and urinary pH, antacids can alter rates of drug dissolution and absorption, bioavailability, and renal elimination (Brunton, supra).

Sixth, because the buffered omeprazole solutions of the prior art require prolonged administration of sodium bicarbonate, it makes it difficult for patients to comply with the regimens of the prior art. For example, Pilbrant et al. disclose an oral omeprazole administration protocol calling for the administration to a subject who has been fasting for at least ten hours, a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later, the subject ingests a suspension of 60 mg of omeprazole in 50 ml of water that also contains 8 mmoles of sodium bicarbonate. This is rinsed down with another 50 ml of 8 mmoles sodium bicarbonate solution. Ten minutes after the ingestion of the omeprazole dose, the subject ingests 50 ml of bicarbonate solution (8 mmoles). This is repeated at twenty minutes and thirty minutes post omeprazole dosing to yield a total of 48 mmoles of sodium bicarbonate and 300 ml of water in total that are ingested by the subject for a single omeprazole dose. Not only does this regimen require the ingestion of excessive amounts of bicarbonate and water, which is likely to be dangerous to some patients, it is unlikely that even healthy patients would comply with this regimen.

It is well documented that patients who are required to follow complex schedules for drug administration are non-compliant and, thus, the efficacy of the buffered omeprazole solutions of the prior art would be expected to be reduced due to non-compliance. Compliance has been found to be markedly reduced when patients are required to deviate from a schedule of one or two (usually morning and night) doses of a medication per day. The use of the prior art buffered omeprazole solutions which require administration protocols with numerous steps, different drugs (sodium bicarbonate+omeprazole+PEG 400 versus sodium bicarbonate alone), and specific time allotments between each stage of the total omeprazole regimen in order to achieve efficacious results is clearly in contrast with both current drug compliance theories and human nature.

The prior art (Pilbrant et al., 1985) teaches that the buffered omeprazole suspension can be stored at refrigerator temperatures for a week and deep frozen for a year while still maintaining 99% of its initial potency. It would be desirable to have an omeprazole or other proton pump inhibitor solution or suspension that could be stored at room temperature or in a refrigerator for periods of time which exceed those of the prior art while still maintaining 99% of the initial potency. Additionally, it would be advantageous to have a form of the omeprazole and bicarbonate which can be utilized to instantly make the omeprazole solution/suspension of the present invention which is supplied in a solid form which imparts the advantages of improved shelf-life at room temperature, lower cost to produce, less expensive shipping costs, and which is less expensive to store.

It would, therefore, be desirable to have a proton pump inhibitor formulation, which provides a cost-effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonists, antacids, and sucralfate. Further, it would be desirable to have a proton pump inhibitor formulation which is convenient to prepare and administer to patients unable to ingest solid dosage forms such as tablets or capsules, which is rapidly absorbed, and can be orally or enterally delivered as a liquid form or solid form. It is desirable that the liquid formulation not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an antacid immediately upon delivery.

It would further be advantageous to have a potentiator or enhancer of the pharmacological activity of the proton pump inhibitors. It has been theorized by applicant that the proton pump inhibitors can only exert their effects on H^+, K^+-ATPase when the parietal cells are active. Accordingly, applicant has identified, as discussed below, parietal cell activators that are administered to synergistically enhance the activity of the proton pump inhibitors.

Additionally, the intravenous dosage forms of proton pump inhibitors of the prior art are often administered in larger doses than the oral forms. For example, the typical adult IV dose of omeprazole is greater than 100 mg/day whereas the adult oral dose is 20 to 40 mg/day. Large IV doses are necessary to achieve the desired pharmacologic effect because, it is believed, many of the parietal cells are in a resting phase (mostly inactive) during an IV dose given to patients who are not taking oral substances by mouth (npo) and, therefore, there is little active (that which is inserted into the secretory canalicular membrane) H^+, K^+-ATPase to inhibit. Because of the clear disparity in the amount of drug necessary for IV versus oral doses, it would be very advantageous to have compositions and methods for IV administration where significantly less drug is required.

SUMMARY OF THE INVENTION AND ADVANTAGES

The foregoing advantages and objects are accomplished by the present invention. The present invention provides an oral solution/suspension comprising a proton pump inhibiting agent and at least one buffering agent. The proton pump inhibiting agent can be any substituted benzimidazole compound having H^+, K^+-ATPase inhibiting activity and being unstable to acid.

The inventive composition can alternatively be formulated as a powder, tablet, suspension tablet, chewable tablet, capsule, two-part tablet or capsule, effervescent powder, effervescent tablet, pellets and granules. Such dosage forms are advantageously devoid of any enteric coating or delayed or sustained-release delivery mechanisms, and comprise a proton pump inhibiting agent and at least one buffering agent to protect the proton pump inhibiting agent against acid degradation. Both the liquid and dry dosage forms can further include anti-foaming agents, parietal cell activators and flavoring agents.

In another embodiment, oral dosage forms are disclosed comprising a combination of enteric-coated or delayed-released proton pump inhibiting agent with an antacid(s). Such forms may optionally comprise a non-enteric-coated proton pump inhibiting agent.

Kits utilizing the inventive dry dosage forms are also disclosed herein to provide for the easy preparation of a liquid composition from the dry forms.

In accordance with the present invention, there is further provided a method of treating gastric acid disorders by orally administering to a patient a pharmaceutical composition(s) and/or dosage form(s) disclosed herein.

Additionally, the present invention relates to a method for enhancing the pharmacological activity of an intravenously administered proton pump inhibiting agent in which at least one parietal cell activator is orally administered to the patient before, during and/or after the intravenous administration of the proton pump inhibiting agent.

Finally, the present invention relates to a method for optimizing the type and amount of buffer desirable for individual proton pump inhibiting agents.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

FIG. 1 is a graph showing the effect of the omeprazole solution of the present invention on gastric pH in patients at risk for upper gastrointestinal bleeding from stress-related mucosal damage;

FIG. 2 is a flow chart illustrating a patient enrollment scheme;

FIG. 3 is a bar graph illustrating gastric pH both pre- and post-administration of omeprazole solution according to the present invention;

FIG. 4 is a graph illustrating the stomach pH values after the oral administration of both ChocoBase plus lansoprazole and lansoprazole alone;

FIG. 5 is a graph illustrating a pH probe confirmation of gastroesophageal reflux disease;

FIG. 6 is a graph illustrating an endoscopic confirmation of gastroesophageal reflux disease;

FIG. 7 is a graph illustrating the percentage of patients who had undergone any type of reflux therapy in the past;

FIG. 8 is a graph illustrating the effectiveness of the Choco-Base Formulation 1; and

FIG. 9 is a graph illustrating the environmental pH values after administration of the proton pump inhibiting agent/buffer formulation.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

The present invention is directed to methods, kits, combinations, and compositions for treating, preventing or reducing the risk of developing a gastrointestinal disorder or disease, or the symptoms associated with, or related to a gastrointestinal disorder or disease in a subject in need thereof.

While the present invention may be embodied in many different forms, several specific embodiments are discussed herein with the understanding that the present disclosure is to be considered only as an exemplification of the principles of the invention, and it is not intended to limit the invention to the embodiments illustrated. For example, where the present invention is illustrated herein with particular reference to omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, or leminoprazole, it will be understood that any other proton pump inhibiting agent, if desired, can be substituted in whole or in part for omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, or leminoprazole in the methods, kits, combinations, and compositions herein described.

The present invention provides a method of increasing absorption of a proton pump inhibiting agent into the blood serum of a subject. The method comprises administering to the subject a solid pharmaceutical composition comprising a proton pump inhibiting agent and a buffering agent for oral administration and ingestion by the subject. Upon administration the composition contacts the gastric fluid of the stomach and thereby increases the absorption of the proton pump inhibiting agent into the blood serum greater than the absorption of the proton pump inhibiting agent in the absence of the buffering agent. The amount of buffering agent present in the composition is sufficient to increase the gastric fluid pH of the stomach to a pH that prevents or inhibits acid degradation of the proton pump inhibiting agent in the gastric fluid of the stomach, and to allow a measurable serum concentration of the proton pump inhibiting agent to be absorbed into the blood serum of the subject. The concentration of the proton pump inhibiting agent can be determined using pharmacokinetic testing procedures known to those skilled in the art.

The present invention also provides for a method of treating a gastrointestinal disorder in a subject in need thereof, by orally administering to the subject a solid pharmaceutical composition comprising a proton pump inhibiting agent and a buffering agent. The buffering agent is in an amount sufficient to increase the pH of the stomach content of the subject to a pH that prevents or inhibits acid degradation of the proton pump inhibiting agent in the stomach and to allow blood serum absorption of the proton pump inhibiting agent greater than the blood serum absorption of the proton pump inhibiting agent in the absence of the buffering agent when the composition is administered orally to the subject. A therapeutically effective amount of proton pump inhibiting agent is thus absorbed into the blood serum of the subject.

The present invention also provides a method of treating an acid related gastrointestinal disorder in a subject in need thereof, by orally administering to the subject a pharmaceutical composition in an oral dosage form for immediate release into an absorption pool of the subject. In one embodiment of the present invention, the absorption pool is highly acidic pH. The composition comprises a proton pump inhibiting agent and a buffering agent. The buffering agent is in an amount sufficient to increase the pH of the absorption pool of the subject to a pH that prevents or inhibits acid degradation of the proton pump inhibiting agent and to allow absorption of the proton pump inhibiting agent from the absorption pool into blood serum of the subject greater than the absorption of the proton pump inhibiting agent in the absence of the buffering agent when the composition is administered orally to the subject. The amount of proton pump inhibiting agent is sufficient to achieve a measurable serum concentration of the proton pump inhibiting agent in the blood serum of the subject after oral administration of the composition.

The present invention also provides a method of making a pharmaceutical composition for oral administration to a subject and for immediate release of a proton pump inhibiting agent and a buffering agent into an absorption pool of the subject. In one embodiment of the present invention the absorption pool is highly acidic pH. The method comprises admixing the proton pump inhibiting agent and the buffering agent. The buffering agent is in an amount sufficient to increase the pH of the absorption pool of the subject to a pH that prevents or inhibits acid degradation of the proton pump inhibiting agent in the absorption pool and to allow absorption of the proton pump inhibiting agent from the absorption pool into blood serum of the subject greater than the absorption of the proton pump inhibiting agent in the

absence of the buffering agent when the composition is administered orally to the subject. The amount of the proton pump inhibiting agent is sufficient to achieve a measurable serum concentration in the blood serum of the subject after oral administration of the composition.

In one embodiment of the present invention, the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1 μg/ml within about 15 minutes after administration of the composition.

In another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1 μg/ml from about 15 minutes to about 6 hours after administration of the composition.

In yet another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15 μg/ml from about 15 minutes to about 1.5 hours after administration of the composition.

In still another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.2 μg/ml within about 15 minutes after administration of the composition.

Besides being useful for human treatment, the present invention is also useful for veterinary treatment of companion mammals, exotic animals and farm animals, including mammals, rodents, and the like. In one embodiment, the mammal includes a horse, dog, or cat.

For the purposes of this application, the term "proton pump inhibitor," or "PPI," or "proton pump inhibiting agent" means any agent possessing pharmacological activity as an inhibitor of H^+, K^+-ATPase. A class of proton pump inhibiting agents useful in the methods, kits, combinations, and compositions of the present invention includes substituted benzimidazole compounds possessing such pharmacological activity as an inhibitor of H^+, K^+-ATPase. In one embodiment of the present invention, the proton pump inhibiting agent is acid sensitive. In another aspect of the invention, the substituted benzimidazole compound employed in the methods, kits, combinations, and compositions can include, for example, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, or leminoprazole. The definition of "PPI," or "proton pump inhibitor," or "proton pump inhibiting agent" as used herein can also mean that the agent possessing pharmacological activity as an inhibitor of H^+, K^+-ATPase may, if desired, be in the form of a salt, ester, amide, enantiomer, isomer, tautomer, prodrug, derivative or the like, provided the salt, ester, amide, enantiomer, isomer, tautomer, prodrug, or derivative is suitable pharmacologically, that is, effective in the present methods, combinations, kits, and compositions. Substituted benzimidazole compounds and the salts, esters, amides, enantiomers, isomers, tautomers, prodrugs and derivatives thereof may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry; Reactions, Mechanisms and Structure,* 4th Ed. (New York: Wiley-Interscience, 1992).

As explained further herein, the proton pump inhibiting agents generally inhibit ATPase in the same way. Differences in onset and relative potencies are largely due to differences in the acid instability of the parent compounds.

In one embodiment, the therapeutic agents of the present invention can be formulated as a single pharmaceutical composition or as independent multiple pharmaceutical dosage forms. Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, buccal (for example, sublingual), or parenteral (for example, intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. Such dosage forms include, but are not limited to, a tablet, a powder, a suspension tablet, a chewable tablet, a capsule, an effervescent powder, an effervescent tablet, a pellet, or a granule.

In one embodiment of the present invention, the compositions comprise a dry formulation, or a solution and/or a suspension of the proton pump inhibiting agent. As used herein, the terms "suspension" and "solution" are interchangeable with each other and generally mean a solution and/or suspension of the substituted benzimidazole in an aqueous medium. Such dry formulations, solutions and/or suspensions may also include, for example, a suspending agent (for example, gums, xanthans, cellulosics and sugars), a humectant (for example, sorbitol), a solubilizer (for example, ethanol, water, PEG and propylene glycol), a surfactant (for example, sodium lauryl sulfate, Spans, Tweens, and cetyl pyridine), a preservative, an antioxidant (for example, parabens, and vitamins E and C), an anti-caking agent, a coating agent, a chelating agent (for example, EDTA), a stabalizer, an antimicrobial agent, an antifungal or antibacterial agent (for example, parabens, chlorobutanol, phenol, sorbic acid), an isotonic agent (for example, sugar, sodium chloride), a thickening agent (for example, methyl cellulose), a flavoring agent (for example, chocolate, thalmantin, aspartame, root beer or watermelon or other flavorings stable at pH 7 to 9), an anti-foaming agent (e.g., simethicone, Mylicon®), a disintegrant, a flow aid, a lubricant, an adjuvant, an excipient, a colorant, a diluent, a moistening agent, a preservative, a pharmaceutically compatible carrier, or a parietal cell activator.

In one embodiment, the present invention relates to a pharmaceutical composition comprising a proton pump inhibiting agent, a buffering agent, and optionally a parietal cell activator. The proton pump inhibitor of the present invention may or may not be enteric coated, or sustained or delayed-release depending on the context in which the proton pump inhibiting agent in utilized. In one embodiment of the present invention the proton pump inhibiting agent is not enteric coated, or sustained or delayed-release. In yet another embodiment the proton pump inhibitor is enteric coated, or sustained or delayed-release. And in another embodiment the composition may contain both an enteric coated proton pump inhibiting agent and a non-enteric coated proton pump inhibiting agent. Such a composition is contemplated where both an immediate release of the proton pump inhibiting agent into the absorption pool is desired as well as a delayed release of the proton pump inhibiting agent is desired providing an extended therapeutic effect.

In still another example, a pharmaceutical formulation is prepared by mixing enteric coated granules of a proton pump inhibiting agent with one or more buffering agents (e.g., omeprazole 20 mg granules plus 500 mg sodium bicarbonate and 500 mg calcium carbonate) in a solid dosage form. Upon oral administration, the buffering agents elevate the gastric pH such that all or part of the enteric coating is dissolved in the gastric fluid (rather than, for example, in the higher pH environment of the duodenum), and the omeprazole is available for immediate release in the gastric fluid for absorption into the bloodstream. Many variations in this type of formulation (i.e., higher or lower

amounts of inhibiting agent and/or buffering agent) may be utilized in the present invention.

After administration to the subject and absorption of the proton pump inhibiting agent (or administration intravenously), the agent is delivered via the blood serum to various tissues and cells of the body including the parietal cells. Not intending to be bound by any one theory, research suggests that when the proton pump inhibiting agent is in the form of a weak base and is non-ionized, it freely passes through physiologic membranes, including the cellular membranes of the parietal cell. It is believed that the non-ionized proton pump inhibiting agent moves into the acid-secreting portion of the parietal cell, the secretory canaliculus. Once in the acidic milieu of the secretory canaliculus, the proton pump inhibiting agent is apparently protonated (ionized) and converted to the active form of the drug. Generally, ionized proton pump inhibiting agents are membrane impermeable and form disulfide covalent bonds with cysteine residues in the alpha subunit of the proton pump. Such active forms are included within the definition of "PPI," "proton pump inhibitor," or "proton pump inhibiting agent" herein.

The proton pump inhibiting agent is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners.

For the purposes of this application, the term "buffering agent" or "buffer" means any pharmaceutically appropriate weak base or strong base (and mixtures thereof) that, when formulated or delivered with (e.g., before, during and/or after) the proton pump inhibiting agent, functions to substantially prevent or inhibit the acid degradation of the proton pump inhibiting agent by gastric acid sufficient to preserve the bioavailability of the proton pump inhibiting agent administered. A buffering agent useful in the methods, kits, combinations, and compositions of the present invention include a bicarbonate salt of Group IA metal, such as, for example, magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, or magnesium silicate. Other buffering agents include, but are not limited to, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, other magnesium salts, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate coprecipitate, a mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Other buffering agents that may be used in the methods, kits, combinations, and compositions of the present invention include, but are not limited to, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium cholride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Mixtures of any of the foregoing can also be used in the methods, kits, combinations, and compositions of the present invention.

The buffering agent is administered in an amount sufficient to substantially prevent or inhibit the acid degradation of the proton pump inhibiting agent by gastric acid sufficient to preserve the bioavailability of the proton pump inhibiting agent administered, and preserve the ability of the proton pump inhibiting agent to elicit a therapeutic effect. Therefore, the buffering agent of the present invention, when in the presence of the biological fluids of the stomach, must only elevate the pH of these biological fluids sufficiently to achieve adequate bioavailability of the drug to effect therapeutic action.

In one embodiment, the buffering agent is present in the methods, kits, combinations, and compositions of the present invention in an amount of about 0.05 mEq to about 5.0 mEq per mg of proton pump inhibiting agent. In another embodiment of the present invention the buffering agent is present in an amount of about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibiting agent. In yet another embodiment of the present invention the buffering agent is present in an amount of at least 10 mEq. In yet another embodiment of the present invention the buffering agent is present in an amount of about 10 mEq to about 70 mEq. In still another embodiment, the buffering agent is present in an amount of about 20 mEq to about 40 mEq. And in yet another embodiment of the present invention, the amount of the buffering agent is present in an amount more than about 20 times the amount of the proton pump inhibiting agent on a weight to weight basis in the composition.

In one embodiment of the present invention, the buffering agent is sodium bicarbonate and is present in the methods, kits, combinations and compositions in an amount of at least 250 mg. In another embodiment, the sodium bicarbonate is present in an amount of at least 800 mg. In yet another embodiment, the sodium bicarbonate is present in an amount from about 250 mg to about 4000 mg. And in still another embodiment, the sodium bicarbonate is present in an amount from about 1000 mg to about 1680 mg.

In one embodiment of the present invention, the buffering agent is calcium carbonate and is present in the methods, kits, combinations and compositions in an amount of at least 250 mg. In another embodiment, the calcium carbonate is present in an amount of at least 800 mg. In yet another embodiment, the calcium carbonate is present in an amount from about 250 mg to about 4000 mg. And in still another embodiment, the calcium carbonate is present in an amount from about 500 mg to about 1000 mg.

The term "effective amount" means, consistent with considerations known in the art, the amount of proton pump inhibiting agent or other agent effective to elicit a pharmacologic effect or therapeutic effect (including, but not limited to, raising of gastric pH, reducing gastrointestinal bleeding, reducing in the need for blood transfusion, improving survival rate, more rapid recovery, parietal cell activation and H^+, K^+-ATPase inhibition or improvement or elimination of symptoms, and other indicators as are selected as appropriate measures by those skilled in the art), without undue adverse side effects.

The term "measurable serum concentration" means the serum concentration (typically measured in mg, µg, or ng of therapeutic agent per ml, dl, or l of blood serum) of a therapeutic agent absorbed into the bloodstream after administration. Illustratively, the serum concentration of a proton pump inhibiting agent of the present invention that corresponds to a measurable serum concentration for an adult subject is greater than about 5 ng/ml. In another embodiment of the present invention, the serum concentration of the proton pump inhibiting agent that corresponds to a measurable serum concentration for an adult human is less than about 10.0 µg/ml. In yet another embodiment of the present

invention, the serum concentration of the proton pump inhibiting agent that corresponds to a measurable serum concentration for an adult human is from about 0.01 μg/ml to about 5 μg/ml. And in still another embodiment of the present invention, the serum concentration of the proton pump inhibiting agent that corresponds to a measurable serum concentration for an adult human is from about 0.25 μg/ml to about 2.5 μg/ml.

In one embodiment of the present invention, the composition is administered to a subject in a therapeutically-effective amount, that is, the composition is administered in an amount that achieves a therapeutically-effective dose of a proton pump inhibiting agent in the blood serum of a subject for a period of time to elicit a desired therapeutic effect. Illustratively, in a fasting adult human (fasting for generally at least 10 hours) the composition is administered to achieve a therapeutically-effective dose of a proton pump inhibiting agent in the blood serum of a subject from about 5 minutes after administration of the composition. In another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 10 minutes from the time of administration of the composition to the subject. In another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 20 minutes from the time of administration of the composition to the subject. In yet another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 30 minutes from the time of administration of the composition to the subject. In still another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 40 minutes from the time of administration of the composition to the subject. In one embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 20 minutes to about 12 hours from the time of administration of the composition to the subject. In another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 20 minutes to about 6 hours from the time of administration of the composition to the subject. In yet another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 20 minutes to about 2 hours from the time of administration of the composition to the subject. In still another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 40 minutes to about 2 hours from the time of administration of the composition to the subject. And in yet another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 40 minutes to about 1 hour from the time of administration of the composition to the subject.

In general, a composition of the present invention is administered at a dose suitable to provide an average blood serum concentration of a proton pump inhibiting agent of at least about 1.0 μg/ml in a subject over a period of about 1 hour after administration. Contemplated compositions of the present invention provide a therapeutic effect as proton pump inhibiting agent medications over an interval of about 5 minutes to about 24 hours after administration, enabling once-a-day or twice-a-day administration if desired. In one embodiment of the present invention, the composition is administered at a dose suitable to provide an average blood serum concentration of a proton pump inhibiting agent of at least about 1.0 μg/ml in a subject about 10, 20, 30, or 40 minutes after administration of the composition to the subject.

The amount of therapeutic agent necessary to elicit a therapeutic effect can be experimentally determined based on, for example, the absorption rate of the agent into the blood serum, the bioavailability of the agent, and the amount of protein binding of the agent. It is understood, however, that specific dose levels of the therapeutic agents of the present invention for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject (including, for example, whether the subject is in a fasting or fed state), the time of A administration, the rate of excretion, the drug combination, and the severity of the particular disorder being treated and form of administration. Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro and/or in vivo tests initially can provide useful guidance on the proper doses for subject administration. Studies in animal models generally may be used for guidance regarding effective dosages for treatment of gastrointestinal disorders or diseases in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular subject, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective in vitro for a period of time effective to elicit a therapeutic effect. Thus, where a compound is found to demonstrate in vitro activity at, for example, 10 ng/ml, one will desire to administer an amount of the drug that is effective to provide at least about a 10 ng/ml concentration in vivo for a period of time that elicits a desired therapeutic effect, for example, raising of gastric pH, reducing gastrointestinal bleeding, reducing the need for blood transfusion, improving survival rate, more rapid recovery, parietal cell activation and H^+, K^+-ATPase inhibition or improvement or elimination of symptoms, and other indicators as are selected as appropriate measures by those skilled in the art. Determination of these parameters is well within the skill of the art. These considerations are well known in the art and are described in standard textbooks.

In order to measure and determine the gastrointestinal disorder- or disease-effective amount of a proton pump inhibiting agent to be delivered to a subject, serum proton pump inhibiting agent concentrations can be measured using standard assay techniques.

"Therapeutic window" refers to the range of plasma concentrations, or the range of levels of therapeutically active substance at the site of action, with a high probability of eliciting a therapeutic effect.

It will be understood that a therapeutically effective amount of a proton pump inhibiting agent and/or a buffering agent that is administered to a subject is dependent inter alia on the body weight of the subject. Illustratively, where the agent is a substituted benzimidazole such as, for example, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, or leminoprazole, and the subject is a child or a small animal (e.g., a dog), for example, a relatively low amount of the agent in the dose range of about

1 mg to about 20 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (e.g., a horse), achievement of such blood serum concentrations of the agent are likely to require dose units containing a relatively greater amount of the agent. For example, in an adult human the methods, kits, combinations, and compositions of the present invention comprise a proton pump inhibiting agent, for example, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, or leminoprazole, in a dosage amount of about 5 mg to about 1000 mg, or of about 7.5 mg to about 300 mg, or of about 10 mg to about 100 mg, or of about 15 mg to about 80 mg.

The solid compositions of the present invention are generally in the form of discrete unit dose articles, such as in a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellet, or granule. Such unit dose articles typically contain about 1 mg to about 1000 mg of the proton pump inhibiting agent, or about 5 mg to about 300 mg, or about 10 mg to about 100 mg, or about 15 mg to about 80 mg. Illustratively, these unit dose articles may contain a 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 75 mg, 80 mg, or 100 mg dose of a proton pump inhibiting agent. In one embodiment, the buffering agent is present in compositions of the present invention in an amount of about 0.05 mEq to about 5.0 mEq per mg of proton pump inhibiting agent, or about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibiting agent, or about 0.5 mEq to about 1.0 mEq per mg of proton pump inhibiting agent. Such dosage units may be given at least once or twice a day, or as many times as needed to elicit a therapeutic response. A particular unit dosage form can be selected to accommodate the desired frequency of administration used to achieve a specified daily dosage.

A pharmaceutical formulation of the proton pump inhibiting agents utilized in the present invention can be administered orally or enterally to the subject. This can be accomplished, for example, by administering the solution via a nasogastric (ng) tube or other indwelling tubes placed in the GI tract. In one embodiment of the present invention, in order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the proton pump inhibiting agent solution of the present invention is administered in a single dose which does not require any further administration of bicarbonate, or other buffer following the administration of the proton pump inhibiting agent solution, nor does it require a large amount of bicarbonate or buffer in total. That is, unlike the prior art proton pump inhibiting agent solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose, which does not require administration of bicarbonate either before or after administration of the proton pump inhibiting agent. The present invention eliminates the need to pre-or post-dose with additional volumes of water and sodium bicarbonate. The amount of bicarbonate administered via the single dose administration of the present invention is less than the amount of bicarbonate administered as taught in the prior art references cited above.

The term "immediate release" is intended to refer to any proton pump inhibiting agent containing formulation in which release of the proton pump inhibiting agent is immediate, i.e., with an "immediate release" formulation, oral administration results in immediate release of the proton pump inhibiting agent into an absorption pool. See also, Remington: The Science and Practice of Pharmacy, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995). As discussed herein, immediate and nonimmediate release (or controlled release) can be defined kinetically by reference to the following equation:

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{K_r} \text{Absorption Pool} \xrightarrow[\text{absorption}]{K_a} \text{Target Area} \xrightarrow[\text{elimination}]{K_e}$$

The absorption pool represents a solution of the drug administered at a particular absorption site, and K_r, K_a, and K_e are first-order rate constants for (1) release of the drug from the formulation, (2) absorption, and (3) elimination, respectively. For immediate release dosage forms, the rate constant for drug release K_r is generally equal to or greater than the absorption rate constant K_a. For controlled release formulations, the opposite is generally true, i.e., $K_r \ll K_a$, such that the rate of release of drug from the dosage form is the rate-limiting step in the delivery of the drug to the target area. The term "controlled release" includes any nonimmediate release formulation, including but not limited to enteric coated formulations and sustained release, delayed release and pulsatile release formulations. The term "sustained release" is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and, may sometimes, although not necessarily, result in substantially constant blood levels of a drug over an extended time period.

"Plasma concentration" refers to the concentration of a substance in blood plasma or blood serum.

"Drug absorption" or "absorption" refers to the process of movement from the site of administration of a drug toward the systemic circulation.

"Bioavailability" refers to the extent to which an active moiety (drug or metabolite) is absorbed into the general circulation and becomes available at the site of drug action in the body.

"Drug elimination" or "elimination" refers to the sum of the processes of drug loss from the body.

"Metabolism" refers to the process of chemical alteration of drugs in the body.

"Pharmacodynamics" refers to the factors which determine the biologic response observed relative to the concentration of drug at a site of action.

"Pharmacokinetics" refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

"Half-life" refers to the time required for the plasma drug concentration or the amount in the body to decrease by 50% from its maximum concentration.

The use of the term "highly acidic pH" in the present disclosure means a pH in the range of about 1 to 4. The use of the term "less acidic to basic pH" in the present disclosure means a pH greater than about 4 up to approximately about 8.0.

The use of the term "about" in the present disclosure means "approximately," and illustratively, the use of the term "about" indicates that dosages slightly outside the cited ranges may also be effective and safe, and such dosages are also encompassed by the scope of the present claims.

The phrase "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited, to appropriate alkali metal salts, alkaline earth metal salts and

other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

The phrase "gastrointestinal disorder" or "gastrointestinal disease" refers generally to a disorder or disease that occurs in a mammal due an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. In mammals, such disorders or diseases include, but are not limited to, duodenal ulcer, gastric ulcer, acid dyspepsia, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, heartburn, other esophageal disorders, and a gastrointestinal pathological hypersecretory condition such as Zollinger Ellison Syndrome. Treatment of these conditions is accomplished by administering to a subject a therapeutically effective amount of a pharmaceutical composition according to the present invention.

The term "treat" or "treatment" as used herein refers to any treatment of a disorder or disease associated with gastrointestinal disorder, and includes, but is not limited to, preventing the disorder or disease from occurring in a mammal which may be predisposed to the disorder or disease, but has not yet been diagnosed as having the disorder or disease; inhibiting the disorder or disease, for example, arresting the development of the disorder or disease; relieving the disorder or disease, for example, causing regression of the disorder or disease; or relieving the condition caused by the disease or disorder, for example, stopping the symptoms of the disease or disorder.

The term "prevent" or "prevention," in relation to a gastrointestinal disorder or disease, means no gastrointestinal disorder or disease development if none had occurred, or no further gastrointestinal disorder or disease development if there had already been development of the gastrointestinal disorder or disease.

The present invention also relates to administration kits to ease mixing and administration. Illustratively, a month's supply of powder or tablets, for example, can be packaged with a separate month's supply of diluent, and a re-usable plastic dosing cup. More specifically, the package could contain thirty (30) suspension tablets containing 20 mg omeprazole each, 1 L sodium bicarbonate 8.4% solution, and a 30 ml dose cup. The user places the tablet in the empty dose cup, fills it to the 30 ml mark with the sodium bicarbonate, waits for it to dissolve (gentle stirring or agitation may be used), and then ingests the suspension. One skilled in the art will appreciate that such kits may contain many different variations of the above components. For example, if the tablets or powder are compounded to contain proton pump inhibiting agent and buffering agent, the diluent may be water, sodium bicarbonate, or other compatible diluent, and the dose cup can be larger or smaller than 30 ml in size. Also, such kits can be packaged in unit dose form, or as weekly, monthly, or yearly kits, etc.

In human therapy, it is important to provide a dosage form that delivers the required therapeutic amount of the drug in vivo, and renders the drug bioavailable in a rapid manner. The formulations of the present invention satisfy these needs.

II. Preparation of Oral Liquids

As described in Phillips U.S. Pat. No. 5,840,737, the liquid oral pharmaceutical composition of the present invention is prepared by mixing omeprazole enteric-coated granules (Prilosec® AstraZeneca), or omeprazole base, or other proton pump inhibitor or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). In one embodiment, omeprazole or other proton pump inhibitor, which can be obtained from powder, capsules, and tablets or obtained from the solution for parenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other proton pump inhibitor) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0 mg/ml. The preferred concentration for the omeprazole in the solution ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml, with 2.0 mg/ml being the standard concentration. For lansoprazole (Prevacid® TAP Pharmaceuticals, Inc.) the concentration can range from about 0.3 mg/ml to 10 mg/ml with the preferred concentration being about 3 mg/ml.

The pharmaceutically acceptable carrier of the oral liquid may comprise a bicarbonate salt of Group IA metal as buffering agent, and can be prepared by mixing the bicarbonate salt of the Group IA metal, preferably sodium bicarbonate, with water. The concentration of the bicarbonate salt of the Group IA metal in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. In one embodiment, the content of the bicarbonate salt of the Group IA metal ranges from about 3 mEq to about 45 mEq per oral dose.

In another embodiment, the amount of sodium bicarbonate 8.4% used in the solution of the present invention is approximately 1 mEq (or mmole) sodium bicarbonate per 2 mg omeprazole, with a range of approximately 0.2 mEq (mmole) to 5 mEq (mmole) per 2 mg of omeprazole.

In an embodiment of the present invention, enterically-coated omeprazole particles are obtained from delayed release capsules (Prilosec® AstraZeneca). Alternatively, omeprazole base powder can be used. The enterically coated omeprazole particles are mixed with a sodium bicarbonate ($NaHCO_3$) solution (8.4%), which dissolves the enteric coating and forms an omeprazole solution.

The inventive solutions and other dosage forms of the present invention have pharmacokinetic advantages over standard enteric-coated and time-released proton pump inhibitor dosage forms, including: (a) more rapid drug absorbance time (about 10 to 60 minutes) following administration for the proton pump inhibitor solution or dry form versus about 1 to 3 hours following administration for the enteric-coated pellets; (b) the buffer solution protects the proton pump inhibitor from acid degradation prior to absorption; (c) the buffer acts as an antacid while the proton pump inhibitor is being absorbed for rapid antacid relief; and (d) the solutions can be administered through an existing indwelling tube without clogging, for example, nasogastric or other feeding tubes jejunal or duodenal), including small bore needle catheter feeding tubes.

Solutions, suspensions and powders for reconstitutable delivery systems include vehicles such as suspending agents (for example, gums, xanthans, celluloses and sugars),

humectants (for example, sorbitol), solubilizers (for example, ethanol, water, PEG and propylene glycol), surfactants (for example, sodium lauryl sulfate, Spans, Tweens, and cetyl pyridine), preservatives and antioxidants (for example, parabens, vitamins E and C, and ascorbic acid), anti-caking agents, coating agents, and chelating agents (for example, EDTA).

Additionally, various additives can be incorporated into the inventive solution to enhance its stability, sterility and isotonicity. Antimicrobial preservatives, such as ambicin, antioxidants, chelating agents, and additional buffers can be added. However, microbiological evidence shows that this formulation inherently possesses antimicrobial and antifungal activity. Various antibacterial and antifungal agents such as, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like can enhance prevention of the action of microorganisms.

In many cases, it would be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Additionally, thickening agents such as methyl cellulose are desirable to use in order to reduce the settling of the omeprazole or other proton pump inhibitor or derivatives thereof from the suspension.

The liquid oral solution may further comprise flavoring agents (e.g., chocolate, thalmantin, aspartame, root beer or watermelon) or other flavorings stable at pH 7 to 9, anti-foaming agents (e.g., simethicone 80 mg, Mylicon®) and parietal cell activators (discussed below).

The present invention further includes a pharmaceutical composition comprising omeprazole or other proton pump inhibitor and derivatives thereof and at least one buffering agent in a form convenient for storage, whereby when the composition is placed into an aqueous solution, the composition dissolves and/or disperses yielding a suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution or suspension in an aqueous solution. The omeprazole or other proton pump inhibiting agents and buffering agent can be formed into a tablet, capsule, pellets or granules, by methods well known to those skilled in the art.

The resultant omeprazole solution is stable at room temperature for several weeks and inhibits the growth of bacteria or fungi as shown in Example X below. Indeed, as established in Example XIII, the solution maintains greater than 90% of its potency for 12 months. By providing a pharmaceutical composition including omeprazole or other proton pump inhibitor with buffer in a solid form, which can be later dissolved or suspended in a prescribed amount of aqueous solution to yield the desired concentration of omeprazole and buffer, the cost of production, shipping, and storage are greatly reduced as no liquids are shipped (reducing weight and cost), and there is no need to refrigerate the solid form of the composition or the solution. Once mixed the resultant solution can then be used to provide dosages for a single subject over a course of time, or for several subjects.

III. Tablets and Other Solid Dosage Forms

As mentioned above, and as described in part in Phillips U.S. Pat. No. 5,840,737, the formulations of the present invention can also be manufactured in concentrated forms, such as powders, capsules, tablets, suspension tablets and effervescent tablets or powders, which can be swallowed whole or first dissolved such that upon reaction with water, gastric secretions or other diluent, the aqueous form of the present invention is produced.

The present pharmaceutical tablets or other solid dosage forms disintegrate rapidly in aqueous media and form an aqueous solution of the proton pump inhibitor and buffering agent with minimal shaking or agitation. Such tablets utilize commonly available materials and achieve these and other desirable objectives. The tablets or other solid dosage forms of this invention provide for precise dosing of a proton pump inhibitor that may be of low solubility in water. They may be particularly useful for medicating children and the elderly and others in a way that is much more acceptable than swallowing or chewing a tablet. The tablets that are produced have low friability, making them easily transportable.

The term "suspension tablets" as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the proton pump inhibitor. The suspension tablets of this invention comprise, in combination, a therapeutic amount of a proton pump inhibitor, a buffering agent, and a disintegrant. More particularly, the suspension tablets comprise about 20 mg omeprazole and about 4–30 mEq of sodium bicarbonate.

Croscarmellose sodium is a known disintegrant for tablet formulations, and is available from FMC Corporation, Philadelphia, Pa. under the trademark Ac-Di-Sol®. It is frequently blended in compressed tableting formulations either alone or in combination with microcrystalline cellulose to achieve rapid disintegration of the tablet.

Microcrystalline cellulose, alone or co processed with other ingredients, is also a common additive for compressed tablets and is well known for its ability to improve compressibility of difficult to compress tablet materials. It is commercially available under the Avicel® trademark. Two different Avicel® products are utilized, Avicel® PH which is microcrystalline cellulose, and Avicel® AC-815, a co processed spray dried residue of microcrystalline cellulose and a calcium-sodium alginate complex in which the calcium to sodium ratio is in the range of about 0.40:1 to about 2.5:1. While AC-815 is comprised of 85% microcrystalline cellulose (MCC) and 15% of a calcium-sodium alginate complex, for purposes of the present invention this ratio may be varied from about 75% MCC to 25% alginate up to about 95% MCC to 5% alginate. Depending on the particular formulation and active ingredient, these two components may be present in approximately equal amounts or in unequal amounts, and either may comprise from about 10% to about 50% by weight of the tablet.

The suspension tablet composition may, in addition to the ingredients described above, contain other ingredients often used in pharmaceutical tablets, including flavoring agents, sweetening agents, flow aids, lubricants or other common tablet adjuvants, as will be apparent to those skilled in the art. Other disintegrants, such as crospovidone and sodium starch glycolate may be employed, although croscarmellose sodium is preferred.

In addition to the suspension tablet, the solid formulation of the present invention can be in the form of a powder, a tablet, a capsule, or other suitable solid dosage form (e.g., a pelleted form or an effervescing tablet, troche or powder), which creates the inventive solution in the presence of diluent or upon ingestion. For example, the water in the stomach secretions or water, which is used to swallow the solid dosage form, can serve as the aqueous diluent.

Compressed tablets are solid dosage forms prepared by compacting a formulation containing an active ingredient and excipients selected to aid the processing and improve the properties of the product. The term "compressed tablet" generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression or by pre-compaction tapping followed by a final compression.

Dry oral formulations can contain excipients such as binders (for example, hydroxypropylmethylcellulose, polyvinyl pyrilodone, other cellulosic materials and starch), diluents (for example, lactose and other sugars, starch, dicalcium phosphate and cellulosic materials), disintegrating agents (for example, starch polymers and cellulosic materials) and lubricating agents (for example, stearates and talc).

Such solid forms can be manufactured as is well known in the art. Tablet forms can include, for example, one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmaceutically compatible carriers. The manufacturing processes may employ one, or a combination of, four established methods: (1) dry mixing; (2) direct compression; (3) milling; and (4) non-aqueous granulation. Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Such tablets may also comprise film coatings, which preferably dissolve upon oral ingestion or upon contact with diluent.

Non-limiting examples of buffering agents which could be utilized in such tablets include sodium bicarbonate, alkali earth metal salts such as calcium carbonate, calcium hydroxide, calcium lactate, calcium glycerophosphate, calcium acetate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide. A particular alkali earth metal salt useful for making an antacid tablet is calcium carbonate.

An example of a low density alkali earth metal salt useful for making the granules according to the present invention is extra light calcium carbonate available from Specialty Minerals Inc., Adams, Me. The density of the extra light calcium carbonate, prior to being processed according to the present invention, is about 0.37 g/ml. Other acceptable buffers are provided throughout this application.

The granules used to make the tablets according to one embodiment of the present invention are made by either spray drying or pre-compacting the raw materials. Prior to being processed into granules by either process, the density of the alkali earth metal salts useful in the present invention ranges from about 0.3 g/ml to about 0.55 g/ml, preferably about 0.35 g/ml to about 0.45 g/ml, even more preferably about 0.37 g/ml to about 0.42 g/ml.

Additionally, the present invention can be manufactured by utilizing micronized compounds in place of the granules or powder. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate. Although micronization results in increased surface area possibly causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole and other proton pump inhibiting agents.

Although the tablets of this invention are primarily intended as a suspension dosage form, the granulations used to form the tablet may also be used to form rapidly disintegrating chewable tablets, lozenges, troches, or swallowable tablets. Therefore, the intermediate formulations as well as the process for preparing them provide additional novel aspects of the present invention.

Effervescent tablets and powders are also prepared in accordance with the present invention. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and tartaric acid. When the salts are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence."

The choice of ingredients for effervescent granules depends both upon the requirements of the manufacturing process and the necessity of making a preparation which dissolves readily in water. The two required ingredients are at least one acid and at least one base. The base releases carbon dioxide upon reaction with the acid. Examples of such acids include, but are not limited to, tartaric acid and citric acid. Preferably, the acid is a combination of both tartaric acid and citric acid. Examples of bases include, but are not limited to, sodium carbonate, potassium bicarbonate and sodium bicarbonate. Preferably, the base is sodium bicarbonate, and the effervescent combination has a pH of about 6.0 or higher.

Effervescent salts preferably include the following ingredients, which actually produce the effervescence: sodium bicarbonate, citric acid and tartaric acid. When added to water the acids and base react to liberate carbon dioxide, resulting in effervescence. It should be noted that any acid-base combination which results in the liberation of carbon dioxide could be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use, and result in a pH of about 6.0 or higher.

It should be noted that it requires 3 molecules of $NaHCO_3$ to neutralize 1 molecule of citric acid and 2 molecules of $NaHCO_3$ to neutralize 1 molecule of tartaric acid. It is desired that the approximate ratio of ingredients is as follows:

Citric Acid:Tartaric Acid:Sodium Bicarbonate=1:2:3.44 (by weight). This ratio can be varied and continue to produce an effective release of carbon dioxide. For example, ratios of about 1:0:3 or 0:1:2 are also effective.

The method of preparation of the effervescent granules of the present invention employs three basic processes: wet and dry granulation, and fusion. The fusion method is used for the preparation of most commercial effervescent powders. It should be noted that although these methods are intended for the preparation of granules, the formulations of effervescent salts of the present invention could also be prepared as tablets, according to well known prior art technology for tablet preparation.

Wet granulation is the oldest method of granule preparation. The individual steps in the wet granulation process of tablet preparation include milling and sieving of the ingredients; dry powder mixing; wet massing; granulation; and final grinding.

Dry granulation involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty rotary tablet press. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillation granulator. The individual steps include mixing of the powders; compressing (slugging); and grinding (slug reduction or granulation). No wet binder or moisture is involved in any of the steps.

The fusion method is the most preferred method for preparing the granules of the present invention. In this method, the compressing (slugging) step of the dry granulation process is eliminated. Instead, the powders are heated in an oven or other suitable source of heat.

IV. Proton Pump Inhibitors Administered with Parietal Cell Activators

Applicant has unexpectedly discovered that certain compounds, such as chocolate, calcium and sodium bicarbonate and other alkaline substances, stimulate the parietal cells and enhance the pharmacologic activity of the proton pump inhibitor administered. For the purposes of this application, "parietal cell activator" or "activator" shall mean any compound or mixture of compounds possessing such stimulatory effect including, but not limited to, chocolate, sodium bicarbonate, calcium (e.g., calcium carbonate, calcium gluconate, calcium hydroxide, calcium acetate and calcium glycerophosphate), peppermint oil, spearmint oil, coffee, tea and colas (even if decaffeinated), caffeine, theophylline, theobromine, and amino acids (particularly aromatic amino acids such as phenylalanine and tryptophan) and combinations thereof, and the salts thereof.

Such parietal cell activators are administered in an amount sufficient to produce the desired stimulatory effect without causing untoward side effects to subjects. For example, chocolate, as raw cocoa, is administered in an amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of other proton pump inhibitor). The dose of activator administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response (i.e., enhanced effect of proton pump inhibitor) over a reasonable time frame. The dose will be determined by the strength of the particular compositions employed and the condition of the person, as well as the body weight of the person to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular composition.

The approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other proton pump inhibitor) are:

Chocolate (raw cocoa)—5 mg to 2.5 g
Sodium bicarbonate—7 mEq to 25 mEq
Calcium carbonate—1 mg to 1.5 g
Calcium gluconate—1 mg to 1.5 g
Calcium lactate—1 mg to 1.5 g
Calcium hydroxide—1 mg to 1.5 g
Calcium acetate—0.5 mg to 1.5 g
Calcium glycerophosphate—0.5 mg to 1.5 g
Peppermint oil—(powdered form) 1 mg to 1 g
Spearmint oil—(powdered form) 1 mg to 1 g
Coffee—20 ml to 240 ml
Tea—20 ml to 240 ml
Cola—20 ml to 240 ml
Caffeine—0.5 mg to 1.5 g
Theophylline—0.5 mg to 1.5 g
Theobromine—0.5 mg to 1.5 g
Phenylalanine—0.5 mg to 1.5 g
Tryptophan—0.5 mg to 1.5 g

Pharmaceutically acceptable carriers are well-known to those who are skilled in the art. The choice of carrier will be determined, in part, both by the particular composition and by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical compositions of the present invention.

V. Examples

The present invention is further illustrated by the following formulations, which should not be construed as limiting in any way. The practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmacology and pharmaceutics, which are within the skill of the art.

Example I

A. Fast Disintegrating Suspension Tablets of Omeprazole.

A fast disintegrating tablet is compounded as follows: Croscarmellose sodium 300 g is added to the vortex of a rapidly stirred beaker containing 3.0 kg of deionized water. This slurry is mixed for 10 minutes. Omeprazole 90 g (powdered) is placed in the bowl of a Hobart mixer. After mixing, the slurry of croscarmellose sodium is added slowly to the omeprazole in the mixer bowl, forming a granulation, which is then placed in trays and dried at 70° C. for three hours. The dry granulation is then placed in a blender, and to it is added 1,500 g of Avicel® AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 1,500 g of Avicel® PH-302 (microcrystalline cellulose). After this mixture is thoroughly blended, 35 g of magnesium stearate is added and mixed for 5 minutes. The resulting mixture is compressed into tablets on a standard tablet press (Hata HS). These tablets have an average weight of about 0.75 g, and contain about 20 mg omeprazole. These tablets have low friability and rapid disintegration time. This formulation may be dissolved in an aqueous solution containing a buffering agent for immediate oral administration.

Alternatively, the suspension tablet may be swallowed whole with a solution of buffering agent. In both cases, the preferred solution is sodium bicarbonate 8.4%. As a further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other proton pump inhibitor) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole with an aqueous diluent.

B1. 10 mg Tablet Formula.

Omeprazole	10 mg (or lansoprazole or pantoprazole or other proton pump inhibitor in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg

B2. 10 mg Tablet Formula.

Proton pump inhibitor: one of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Other proton pump inhibitor in an equipotent amount	
Calcium lactate	375 mg
Calcium glycerophosphate	375 mg
Aspartame calcium (phenylalanine)	0.5 mg

-continued

Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg

B3. 10 mg Tablet Formula.

Proton pump inhibitor: one of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Other proton pump inhibitor in an equipotent amount	
Sodium bicarbonate	750 mg
Aspartame sodium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg

C1. 20 mg Tablet Formula.

Omeprazole	20 mg (or lansoprazole or pantoprazole or other proton pump inhibitor in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Calcium hydroxide	10 mg
Peppermint	3 mg
Maltodextrin	3 mg
Mannitol	3 mg
Pregelatinized starch	3 mg

C2. 20 mg Tablet Formula.

Proton pump inhibitor: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Other proton pump inhibitor in an equipotent amount	
Calcium lactate	375 mg
Calcium glycerophosphate	375 mg
Aspartame calcium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg

C3. 20 mg Tablet Formula.

Proton pump inhibitor: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg

-continued

Other proton pump inhibitor in an equipotent amount	
Sodium bicarbonate	750 mg
Aspartame sodium (phenylalanine)	0.5 mg
Colloidal silicon dioxide	12 mg
Corn starch	15 mg
Croscarmellose sodium	12 mg
Dextrose	10 mg
Peppermint	3 mg
Maltodextrin	20 mg
Mannitol	30 mg
Pregelatinized starch	30 mg

D1. Tablet for Rapid Dissolution.

Omeprazole	20 mg (or lansoprazole or pantoprazole or other proton pump inhibitor in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Croscarmellose sodium	12 mg

D2. Tablet for Rapid Dissolution.

Proton pump inhibitor: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg
Other proton pump inhibitor in an equipotent amount	
Calcium lactate	300 mg
Calcium glycerophosphate	300 mg
Calcium hydroxide	50 mg
Croscarmellose sodium	12 mg

D3. Tablet for Rapid Dissolution.

Proton pump inhibitor: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg
Other proton pump inhibitor in an equipotent amount	
Sodium bicarbonate	700 mg
Trisodium phosphate dodecahydrate	100 mg
Croscarmellose sodium	12 mg

E1. Powder for Reconstitution for Oral Use (or per ng tube).

Omeprazole	20 mg (or lansoprazole or pantoprazole or other proton pump inhibitor in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	500 mg
Calcium hydroxide	50 mg
Glycerine	200 mg

E2. Powder for Reconstitution for Oral Use (or per ng tube).

Proton pump inhibitor: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg

-continued

Other proton pump inhibitor in an equipotent amount	
Calcium lactate	300 mg
Calcium glycerophosphate	300 mg
Calcium hydroxide	50 mg
Glycerine	200 mg

E3. Powder for Reconstitution for Oral Use (or per ng tube).

Proton pump inhibitor: One of the following:	
Omeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg
Rabeprazole sodium	20 mg
Esomeprazole magnesium	20 mg
Other proton pump inhibitor in an equipotent amount	
Sodium bicarbonate	850 mg
Trisodium phosphate	50 mg

F1. 10 mg Tablet Formula.

Omeprazole	10 mg (or lansoprazole or pantoprazole or other proton pump inhibitor in an equipotent amount)
Calcium lactate	175 mg
Calcium glycerophosphate	175 mg
Sodium bicarbonate	250 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	1 mg
Magnesium stearate	1 mg

F2. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other proton pump inhibitor in an equipotent amount	
Calcium lactate	475 mg
Calcium glycerophosphate	250 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	10 mg
Magnesium stearate	10 mg

F3. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other proton pump inhibitor in an equipotent amount	
Sodium bicarbonate	700 mg
Polyethylene glycol	20 mg
Croscarmellose sodium	12 mg
Peppermint	3 mg
Magnesium silicate	10 mg
Magnesium stearate	10 mg

-continued

G1. 10 mg Tablet Formula.

Omeprazole	10 mg (or lansoprazole or pantoprazole or other proton pump inhibitor in an equipotent amount)
Calcium lactate	200 mg
Calcium glycerophosphate	200 mg
Sodium bicarbonate	400 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg

G2. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other proton pump inhibitor in an equipotent amount	
Calcium lactate	400 mg
Calcium glycerophosphate	400 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg

G3. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:	
Omeprazole	10 mg
Lansoprazole	15 mg
Pantoprazole sodium	20 mg
Rabeprazole sodium	10 mg
Esomeprazole magnesium	10 mg
Other proton pump inhibitor in an equipotent amount	
Sodium bicarboante	750 mg
Croscarmellose sodium	12 mg
Pregelatinized starch	3 mg

All of the tablets and powders of this Example may be swallowed whole, chewed or mixed with an aqueous medium prior to administration.

Example II

Standard Tablet of Proton Pump Inhibitor and Buffering Agent.

Ten (10) tablets were prepared using a standard tablet press, each tablet comprising about 20 mg omeprazole and about 975 mg sodium bicarbonate uniformly dispersed throughout the tablet. To test the disintegration rate of the tablets, each was added to 60 ml of water. Using previously prepared liquid omeprazole/sodium bicarbonate solution as a visual comparator, it was observed that each tablet was completely dispersed in under three (3) minutes.

Another study using the tablets compounded according to this Example evaluated the bioactivity of the tablets in five (5) adult critical care subjects. Each subject was administered one tablet via ng with a small amount of water, and the pH of ng aspirate was monitored using paper measure. The pH for each subject was evaluated for 6 hours and remained above 4, thus demonstrating the therapeutic benefit of the tablets in these patients.

Tablets were also prepared by boring out the center of sodium bicarbonate USP 975 mg tablets with a knife. Most of the removed sodium bicarbonate powder was then triturated with the contents of a 20 mg Prilosec® capsule and the resulting mixture was then packed into the hole in the tablet and sealed with glycerin.

Example III

Proton Pump Inhibitor Central Core Tablet.

Tablets are prepared in a two-step process. First, about 20 mg of omeprazole is formed into a tablet as is known in the art to be used as a central core. Second, about 975 mg sodium bicarbonate USP is used to uniformly surround the central core to form an outer protective cover of sodium bicarbonate. The central core and outer cover are both prepared using standard binders and other excipients to create a finished, pharmaceutically acceptable tablet. The tablets may be swallowed whole with a glass of water.

Example IV

Effervescent Tablets and Granules.

The granules of one 20 mg Prilosec® capsule were emptied into a mortar and triturated with a pestle to a fine powder. The omeprazole powder was then geometrically diluted with about 958 mg sodium bicarbonate USP, about 832 mg citric acid USP and about 312 mg potassium carbonate USP to form a homogeneous mixture of effervescent omeprazole powder. This powder was then added to about 60 ml of water whereupon the powder reacted with the water to create effervescence. A bubbling solution resulted of omeprazole and principally the antacids sodium citrate and potassium citrate. The solution was then administered orally to one adult male subject and gastric pH was measured using pHydrion paper. The results were as follows:

Time Interval	pH Measured
Immediately prior to dose	2
1 hour post dose	7
2 hours post dose	6
4 hours post dose	6
6 hours post dose	5
8 hours post dose	4

One skilled in the art of pharmaceutical compounding will appreciate that bulk powders can be manufactured using the above ratios of ingredients, and that the powder can be pressed into tablets using standard binders and excipients. Such tablets are then mixed with water to activate the effervescent agents and create the desired solution. In addition, lansoprazole 30 mg (or an equipotent dose of other proton pump inhibitor) can be substituted for omeprazole.

The effervescent powder and tablets can alternatively be formulated by employing the above mixture but adding an additional 200 mg of sodium bicarbonate USP to create a resulting solution with a higher pH. Further, instead of the excess 200 mg of sodium bicarbonate, 100 mg of calcium glycerophosphate or 100 mg of calcium lactate can be employed. Combinations of the same can also added.

Example V

Parietal Cell Activator "Choco-Base™" Formulations and Efficacy.

Children are affected by gastro esophageal reflux disease (GERD) with atypical manifestations. Many of these atypical symptoms are difficult to control with traditional drugs such as H_2-antagonists, cisapride, or sucralfate. Proton pump inhibiting agents are more effective in controlling gastric pH and the symptoms of gastroesophageal reflux disease than other agents. However, proton pump inhibiting agents are not available in dosage forms that are easy to administer to young children. To address this problem, applicant employed omeprazole or lansoprazole in a buffered chocolate suspension (Choco-Base), in children with manifestations of gastroesophageal reflux disease.

Applicant performed a retrospective evaluation of children with gastroesophageal reflux disease referred to the University of Missouri-Columbia from 1995 to 1998 who received treatment with the experimental omeprazole or lansoprazole Choco-Base suspension formulated in accordance with Formulation 1 stated below. Data were included on all patients with follow up information sufficient to draw conclusions about pre/post treatment (usually >6 months). There were 25 patients who met the criteria for this evaluation. Age range was several weeks to greater than 5 years. Most patients had a history of numerous unsuccessful attempts at ameliorating the effects of gastroesophageal reflux disease. Medication histories indicated many trials of various drugs.

The primary investigator reviewed all charts for uniformity of data collection. When insufficient data was available in the University charts, attempts were made to review charts in the local primary care physicians' offices for follow-up data. If information was still unavailable to review, attempts were made to contact family for follow-up. If data were still unavailable the patients were considered inevaluable.

Patient charts were reviewed in detail. Data noted were date of commencement of therapy, date of termination of therapy and any reason for termination other than response to treatment. Patient demographics were also recorded, as were any other medical illnesses. Medical illnesses were divided grossly into those that are associated with or exacerbate gastroesophageal reflux disease and those that do not.

Patient charts were examined for evidence of response to therapy. As this was largely a referral population, and a retrospective review, quantification of symptomatology based on scores, office visits and ED visits was difficult. Therefore, applicant examined charts for evidence of an overall change in patient symptoms. Any data to point towards improvement, decline or lack of change were examined and recorded.

Results.

A total of 33 pediatric patients to date have been treated with the above-described suspension at the University of Missouri—Columbia. Of the 33 patients, 9 were excluded from the study, all based upon insufficient data about commencement, duration or outcome in treatment with proton pump inhibitor therapy. This left 24 patients with enough data to draw conclusions.

Of the 24 remaining patients, 18 were males and 6 females. Ages at implementation of proton pump inhibitor therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months [mean of 37 mo.]. Early on, reflux was usually documented by endoscopy and confirmed by pH probe. Eventually, pH probe was dropped and endoscopy was the sole method for documenting reflux, usually at the time of another surgery (most often T-tubes or adenoidectomy). Seven patients had pH probe confirmation of gastroesophageal reflux disease, whereas 18 had endoscopic confirmation of reflux including all eight who had pH probing done (See FIGS. 5 and 6). Reflux was diagnosed on endoscopy most commonly by cobblestoning of the tracheal wall, with laryngeal and pharyngeal cobblestoning as findings in a few patients. Six patients had neither pH nor endoscopic documentation of gastroesophageal reflux disease, but were tried on proton pump inhibitor therapy based on symptomatology alone.

Past medical history was identified in each chart. Ten patients had reflux-associated diagnoses. These were most commonly cerebral palsy, prematurity and Pierre Robin sequence. Other diagnoses were Charcot-Marie-Tooth

disease, Velocardiofacial syndrome, Down syndrome and De George's syndrome. Non-reflux medical history was also identified and recorded separately (See Table 2 below).

Patients were, in general, referral patients from local family practice clinics, pediatricians, or other pediatric health care professionals. Most patients were referred to ENT for upper airway problems, sinusitis, or recurrent/chronic otitis media that had been refractory to medical therapy as reported by the primary care physician. Symptoms and signs most commonly found in these patients were recorded and tallied. All signs and symptoms were broken down into six major categories: (1) nasal; (2) otologic; (3) respiratory; (4) gastrointestinal; (5) sleep-related; and (6) other. The most common problems fell into one or all of the first 3 categories (See Table 1 below).

Most patients had been treated in the past with medical therapy in the form of antibiotics, steroids, asthma medications and other diagnosis-appropriate therapies. In addition, nine of the patients had been on reflux therapy in the past, most commonly in the form of conservative therapy such as head of bed elevation 300, avoidance of evening snacks, avoidance of caffeinated beverages as well as cisapride and ranitidine (See FIG. 7).

The proton pump inhibitor suspension used in this group of patients was Choco-Base suspension of either lansoprazole or omeprazole. The dosing was very uniform, with patients receiving doses of either 10 or 20 mg of omeprazole and 23 mg of lansoprazole. Initially, in April of 1996 when therapy was first instituted 10 mg of omeprazole was used. There were 3 patients in this early phase who were treated initially with 10 mg po qd of omeprazole. All three subsequently were increased to either 20 mg po qd of omeprazole or 23 mg po qd of lansoprazole. All remaining patients were given either the 20 mg omeprazole or the 23 mg lansoprazole treatment qd, except in one case, where 30 mg of lansoprazole was used. Patients were instructed to take their doses once per day, preferably at night in most cases. Suspensions were all filled through the University of Missouri Pharmacy at Green Meadows. This allowed for tracking of usage through refill data.

Most patients responded favorably to and tolerated the once daily dosing of Choco-Base proton pump inhibitor suspension. Two patients had documented adverse effects associated with the use of the proton pump inhibitor suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment failure. The other patient had small amounts of bloody stools per mother. This patient never had his stool tested, as his bloody stool promptly resolved upon cessation of therapy, with no farther sequellae. The other 23 patients had no documented adverse effects.

Patients were categorized based on review of clinic notes and chart review into general categories: (1) improved; (2) unchanged; (3) failed; and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of proton pump inhibitor therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical findings while on therapy, one complained of worsening symptoms while on therapy, one patient had therapy as prophylaxis for surgery, and two stopped therapy just after its commencement (see FIG. 8). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which proton pump inhibitor therapy was for purely prophylactic reasons, leaves (17/21) 81% of patients that responded to Choco-Base suspension. This means that 19% (4/21) of patients received no apparent benefit from proton pump inhibitor therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were mild bloody stool that completely resolved upon cessation of therapy.

Discussion.

Gastroesophageal reflux disease in the pediatric population is relatively common, affecting almost 50% of newborns. Even though most infants outgrow physiologic reflux, pathologic reflux still affects approximately 5% of all children throughout childhood. Recently considerable data has pointed to reflux as an etiologic factor in extra-esophageal areas. gastroesophageal reflux disease has been attributed to sinusitis, dental caries, otitis media, asthma, apnea, arousal, pneumonia, bronchitis, and cough, among others. Despite the common nature of reflux, there seems to have been little improvement in therapy for reflux, especially in the non-surgical arena.

The standard of therapy for the treatment of gastroesophageal reflux disease in the pediatric population has become a progression from conservative therapy to a combination of a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, proton pump inhibitor therapy is effective in 90% of those treated for gastroesophageal reflux disease. As a medical alternative to the H-2 blockers, the proton pump inhibiting agents have not been studied extensively in the pediatric population. Part of the reason for this lack of data may be related to the absence of a suitable dosage formulation for this very young population, primarily under 2 years of age, that does not swallow capsules or tablets. It would be desirable to have a true liquid formulation (solution or suspension) with good palatability such as is used for oral antibiotics, decongestants, antihistamines, H-2 blockers, cisapride, metoclopramide, etc. The use of lansoprazole granules (removed from the gelatin capule) and sprinkled on applesauce has been approved by the Food and Drug Administration as an alternative method of drug administration in adults but not in children. Published data are lacking on the efficacy of the lansoprazole sprinkle method in children. Omeprazole has been studied for bioequivalence as a sprinkle in adults and appears to produce comparable serum concentrations when compared to the standard capsule. Again no data are available on the omeprazole sprinkle in children. An additional disadvantage of omeprazole is its taste which is quinine-like. Even when suspended in juice, applesauce or the like, the bitter nature of the medicine is easily tasted even if one granule is chewed. For this reason applicant eventually progressed to use lansoprazole in Choco-Base. Pantoprazole and rabeprazole are available as enteric-coated tablets only. Currently, none of the proton pump inhibiting agents available in the United States are approved for pediatric use. There is some controversy as to what the appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective proton pump inhibitor dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity with the proton pump inhibiting agents is not seen even at >50 mg/kg, there appears little risk associated with the higher dosages. Based on observations at the University of Missouri consistent with the findings of this review, applicant established a simple fixed dosage regimen of 10 ml Choco-Base suspension daily. This 10 ml dose provided 20 mg omeprazole or 23 mg lansoprazole.

In the ICU setting, the University of Missouri-Columbia has been using an unflavored proton pump inhibitor suspen-

sion given once daily per various tubes (nasogastric, g-tube, jejunal feeding tube, duo tube, etc.) for stress ulcer prophylaxis. It seemed only logical that if this therapy could be made into a palatable form, it would have many ideal drug characteristics for the pediatric population. First, it would be liquid, and therefore could be administered at earlier ages. Second, if made flavorful it could help to reduce noncompliance. Third, it could afford once daily dosing, also helping in reducing noncompliance. In the process, applicant discovered that the dosing could be standardized, which nearly eliminated dosing complexity.

Choco-Base is a product which protects drugs which are acid labile, such as proton pump inhibiting agents, from acid degradation. The first few pediatric patients with reflux prescribed Choco-Base were sicker patients. They had been on prior therapy and had been diagnosed both by pH probe and endoscopy. In the first few months, applicant treated patients with 10 mg of omeprazole qd (1 mg/kg) and found this to be somewhat ineffective, and quickly increased the dosing to 20 mg (2 mg/kg) of omeprazole. About halfway through the study, applicant began using lansoprazole 23 mg po qd. Applicant's standard therapy was then either 20 mg of omeprazole or 23 mg of lansoprazole once daily. The extra 3 mg of lansoprazole is related only to the fact that the final concentration was 2.25 mg/ml, and applicant desired to keep dosing simple, so he used a 10 ml suspension.

The patients that were treated represented a tertiary care center population, and they were inherently sicker and refractory to medical therapy in the past. The overall 72% success rate is slightly lower than the 90% success rates of proton pump inhibiting agents in the adult population, but this can be attributed to the refractory nature of their illness, most having failed prior non-proton pump inhibitor treatment. The population in this study is not indicative of general practice populations.

Conclusion.

Proton pump inhibitor therapy is a beneficial therapeutic option in the treatment of reflux related symptoms in the pediatric population. Its once daily dosing and standard dosing scheme combined with a palatable formulation makes it an ideal pharmacologic agent.

TABLE 1

Symptoms	Patient Numbers
Nasal:	35
Sinusitis	7
Congestion	8
Nasal discharge	16
Other	4
Otologic:	26
Otitis Media	17
Otorrhea	9
Respiratory:	34
Cough	10
Wheeze	11
Respiratory Distress:	5
Pneumonia	2
Other	6
Gastrointestinal:	10
Abdominal Pain	1
Reflux/Vomiting	4
Other	4
Sleep Disturbances:	11
Other	2

TABLE 2

Reflux Associated:	12
Premature	5
Pierre-Robin	2
Cerebral Palsy	2
Down Syndrome	1
Charcot-Marie-Tooth	1
Velocardiofacial Syndrome	1
Other Medical History	12
Cleft Palate	3
Asthma	3
Autism	2
Seizure Disorder	1
Diabetes Mellitus	1
Subglottic Stenosis	1
Tracheostomy Dependent	1

FORMULATION 1

PART A INGREDIENTS	AMOUNT (mg)
Omeprazole	200
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT (ml)**
Distilled Water	100

COMPOUNDING INSTRUCTIONS

Add Part B to Part A to create a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.

FORMULATION 2

PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	**AMOUNT**
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg

COMPOUNDING INSTRUCTIONS

Mix the constituents of Part B together thoroughly and then add to Part A. This results in a total volume of approximately 130 ml with an omeprazole concentration of about 1.5 mg/ml.

FORMULATION 3	
PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Sodium Bicarbonate	9400
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	AMOUNT
Distilled Water	100 ml
Omeprazole	200 mg
COMPOUNDING INSTRUCTIONS	
This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.	

FORMULATION 4	
PART A INGREDIENTS (mg)	AMOUNT (mg)
Sucrose	26000
Cocoa	1800
Corn Syrup Solids	6000
Sodium Caseinate	1000
Soy Lecithin	150
Sodium Chloride	35
Tricalcium Phosphate	20
Dipotassium Phosphate	12
Silicon Dioxide	5
Sodium Stearoyl Lactylate	5
PART B INGREDIENTS	AMOUNT
Distilled Water	100 ml
Sodium Bicarbonate	8400 mg
Omeprazole	200 mg
COMPOUNDING INSTRUCTIONS	
This formulation is reconstituted at the time of use by a pharmacist. Part B is mixed first and is then uniformly mixed with the components of Part A. A final volume of about 130 ml is created having an omeprazole concentration of about 1.5 mg/ml.	

In all four of the above formulations, lansoprazole or other proton pump inhibitor can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200 mg of omeprazole. Additionally, aspartame can be substituted for sucrose, and the following other ingredients can be employed as carriers, adjuvants and excipients: maltodextrin, vanilla, carrageenan, mono and diglycerides, and lactated monoglycerides. One skilled in the art will appreciate that not all of the ingredients are necessary to create a Choco-Base formulation that is safe and effective.

Omeprazole powder or enteric-coated granules can be used in each formulation. If the enteric-coated granules are used, the coating is either dissolved by the aqueous diluent or inactivated by trituration in the compounding process.

Applicant additionally analyzed the effects of a lansoprazole Choco-Base formulation on gastric pH using a pH meter (Fisher Scientific) in one adult patient versus lansoprazole alone. The patient was first given a 30 mg oral capsule of lansoprazole (Prevacid®), and the patient's gastric pH was measured at 0, 4, 8, 12, and 16 hours post dose. The results are illustrated in FIG. 4.

The ChocoBase product was compounded according to Formulation 1 above, except 300 mg of lansoprazole was used instead of omeprazole. A dose of 30 mg lansoprazole Choco-Base was orally administered at hour 18 post lansoprazole alone. Gastric pH was measured using a pH meter at hours 18, 19, 24, 28, 32, 36, 40, 48, 52, and 56 post lansoprazole alone dose.

FIG. 4 illustrates the lansoprazole/cocoa combination resulted in higher pH, at hours 19–56 than lansoprazole alone at hours 4–18. Therefore, the combination of the lansoprazole with chocolate enhanced the pharmacologic activity of the lansoprazole. The results establish that the sodium bicarbonate as well as chocolate flavoring and calcium were all able to stimulate the activation of the proton pumps, perhaps due to the release of gastrin. Proton pump inhibiting agents work by functionally inhibiting the proton pump and effectively block activated proton pumps (primarily those inserted into the secretory canalicular membrane). By further administering the proton pump inhibitor with one of these activators or enhancers, there is a synchronization of activation of the proton pump with the absorption and subsequent parietal cell concentrations of the proton pump inhibitor. As illustrated in FIG. 4, this combination produced a much longer pharmacologic effect than when the proton pump inhibitor was administered alone.

Example VI

Combination Tablet Delivering Bolus And Time-Released Doses of Proton Pump Inhibitor

Tablets were compounded using known methods by forming an inner core of 10 mg omeprazole powder mixed with 750 mg sodium bicarbonate, and an outer core of 10 mg omeprazole enteric-coated granules mixed with known binders and excipients. Upon ingestion of the whole tablet, the tablet dissolves and the inner core is dispersed in the stomach where it is absorbed for immediate therapeutic effect. The enteric-coated granules are later absorbed in the duodenum to provide symptomatic relief later in the dosing cycle. This tablet is particularly useful in patients who experience breakthrough gastritis between conventional doses, such as while sleeping or in the early morning hours.

Example VII

Therapeutic Application.

Patients were evaluable if they met the following criteria: had two or more risk factors for SRMD (mechanical ventilation, head injury, severe burn, sepsis, multiple trauma, adult respiratory distress syndrome, major surgery, acute renal failure, multiple operative procedures, coagulotherapy, significant hypertension, acid-base disorder, and hepatic failure), gastric pH of ≦4 prior to study entry, and no concomitant prophylaxis for SRMD.

The omeprazole solution was prepared by mixing 10 ml of 8.4% sodium bicarbonate with the contents of a 20 mg capsule of omeprazole (Merck & Co. Inc., West Point, Pa.) to yield a solution having a final omeprazole concentration of 2 mg/ml.

Nasogastric (ng) tubes were placed in the patients and an omeprazole dosage protocol of buffered 40 mg omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$–8.4%) followed by 40 mg of the same buffered omeprazole solution in eight

hours, then 20 mg of the same buffered omeprazole solution per day, for five days. After each buffered omeprazole solution administration, nasogastric suction was turned off for thirty minutes.

Eleven patients were evaluable. All patients were mechanically ventilated. Two hours after the initial 40 mg dose of buffered omeprazole solution, all patients had an increase in gastric pH to greater than eight as shown in FIG. 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four when administered 20 mg omeprazole solution. One patient required 40 mg omeprazole solution per day (closed head injury, five total risk factors for SRMD). Two patients were changed to omeprazole solution after having developed clinically significant upper gastrointestinal bleeding while receiving conventional intravenous H_2-antagonists. Bleeding subsided in both cases after twenty-four hours. Clinically significant upper gastrointestinal bleeding did not occur in the other nine patients. Overall mortality was 27%, mortality attributable to upper gastrointestinal bleeding was 0%. Pneumonia developed in one patient after initiating omeprazole therapy and was present upon the initiation of omeprazole therapy in another patient. The mean length of prophylaxis was five days.

A pharmacoeconomic analysis revealed a difference in the total cost of care for the prophylaxis of SRMD:

- ranitidine (Zantac®) continuous infusion intravenously (150 mg/24 hours)xfive days $125.50;
- cimetidine (Tagamet®) continuous infusion intravenously (900 mg/24 hours)xfive days $109.61;
- sucralfate one g slurry four times a day per (ng) tubexfive days $73.00; and
- buffered omeprazole solution regimen per (ng) tubexfive days $65.70.

This example illustrates the efficacy of the buffered omeprazole solution of the present invention based on the increase in gastric pH, safety and cost of the buffered omeprazole solution as a method for SRMD prophylaxis.

Example VIII

Effect on pH.

Experiments were carried out in order to determine the effect of the omeprazole solution (2 mg omeprazole/1 ml $NaHCO_3$-8.4%) administration on the accuracy of subsequent pH measurements through a nasogastric tube.

After preparing a total of 40 mg of buffered omeprazole solution, in the manner of Example VII, doses were administered into the stomach, usually through a nasogastric (ng) tube. Nasogastric tubes from nine different institutions were gathered for an evaluation. Artificial gastric fluid (gf) was prepared according to the USP. pH recordings were made in triplicate using a Microcomputer Portable pH meter model 6007 (Jenco Electronics Ltd., Taipei, Taiwan).

First, the terminal portion (tp) of the nasogastric tubes was placed into a glass beaker containing the gastric fluid. A 5 ml aliquot of gastric fluid was aspirated through each tube and the pH recorded; this was called the "pre-omeprazole solution/suspension measurement." Second, the terminal portion (tp) of each of the nasogastric tubes was removed from the beaker of gastric fluid and placed into an empty beaker. Twenty (20) mg of omeprazole solution was delivered through each of the nasogastric tubes and flushed with 10 ml of tap water. The terminal portion (tp) of each of the nasogastric tubes was placed back into the gastric fluid. After a one hour incubation, a 5 ml aliquot of gastric fluid was aspirated through each nasogastric tube and the pH recorded; this was called the "after first dose SOS [Simplified Omeprazole Solution] measurement." Third, after an additional hour had passed, the second step was repeated; this was called the "after second dose SOS [Simplified Omeprazole Solution] measurement." In addition to the pre-omeprazole measurement, the pH of the gastric fluid was checked in triplicate after the second and third steps. A change in the pH measurements of +/−0.3 units was considered significant. The Friedman test was used to compare the results. The Friedman test is a two way analysis of variance which is used when more than two related samples are of interest, as in repeated measurements.

The results of these experiments are outlined in Table 3.

TABLE 3

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
[1] gf Pre SOS	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[2] gf p 1st dose 1.3↑ check of gf pH	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[3] gf p 2nd Dose 1.3↑ check of gf pH	1.3	1.3	1.4	1.4	1.4	1.3	1.4	1.3	1.3
								SOS pH = 9.0	

Table 3 illustrates the results of the pH measurements that were taken during the course of the experiment. These results illustrate that there were no statistically significant latent effects of omeprazole solution administration (per nasogastric tube) on the accuracy of subsequent pH measurements obtained through the same nasogastric tube.

Example IX

Efficacy of Buffered Omeprazole Solution in Ventilated Patients.

Experiments were performed in order to determine the efficacy, safety, and cost of buffered omeprazole solution in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Patients: Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage.

Interventions: Patients received 20 ml omeprazole solution (prepared as per Example VII and containing 40 mg of omeprazole) initially, followed by a second 20 ml dose six to eight hours later, then 10 ml (20 mg) daily. Omeprazole solution according to the present invention was administered through a nasogastric tube, followed by 5–10 ml of tap water. The nasogastric tube was clamped for one to two hours after each administration.

Measurements and Main Results: The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage and was associated with a five percent decrease in hematocrit. Secondary efficacy measures were gastric pH measured four hours after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the incidence of adverse events and the incidence of pneumonia. No patient experienced clinically significant upper gastrointestinal

bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric pH was 7.1 (mean), the mean gastric pH after starting omeprazole was 6.8 (mean) and the lowest pH after starting omeprazole was 5.6 (mean). The incidence of pneumonia was twelve percent. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions: Omeprazole solution prevented clinically significant upper gastrointestinal bleeding and maintained gastric pH above 5.5 in mechanically ventilated critical care patients without producing toxicity.

Materials and Methods:

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population: All adult (>18 years old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated intensive care unit stay of at least forty-eight hours were considered for inclusion in the study. To be included patients also had to have a gastric pH of <4, had to be mechanically ventilated and have one of the following additional risk factors for a minimum of twenty-four hours after initiation of omeprazole suspension: head injury with altered level of consciousness, extensive burns (>20% Body Surface Area), acute renal failure, acid-base disorder, multiple trauma, coagulopathy, multiple operative procedures, coma, hypotension for longer than one hour or sepsis (see Table 4). Sepsis was defined as the presence of invasive pathogenic organisms or their toxins in blood or tissues resulting in a systematic response that included two or more of the following: temperature greater than 38° C. or less than 36° C., heart rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute (or $_pO_2$ less than 75 mm Hg), and white blood cell count greater than 12,000 or less than 4,000 cells/mm^3 or more than 10 percent bands (Bone, *Let's Agree on Terminology: Definitions of Sepsis,* CRIT. CARE MED., 19:27 (1991)). Patients in whom H_2-antagonist therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count less than 30,000 cells/mm^3); were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH above four for forty-eight hours after ICU admission (without prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having non-stress-related mucosal bleeding. The reason for this exclusion is the confounding effect of non-stress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration: Omeprazole solution was prepared immediately before administration by the patient's nurse using the following instructions: empty the contents of one or two 20 mg omeprazole capsule(s) into an empty 10 ml syringe (with 20 gauge needle in place) from which the plunger has been removed. (Omeprazole delayed-release capsules, Merck & Co., Inc., West Point, Pa.); replace the plunger and uncap the needle; withdraw 10 ml of 8.4% sodium bicarbonate solution or 20 ml if 40 mg given (Abbott Laboratories, North Chicago, Ill.), to create a concentration of 2 mg omeprazole per ml of 8.4% sodium bicarbonate; and allow the enteric coated pellets of omeprazole to completely breakdown, 30 minutes (agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before administration. The solution was not administered with acidic substances. A high-pressure liquid chromatography study was performed that demonstrated that this preparation of simplified omeprazole suspension maintains>90% potency for seven days at room temperature. This preparation remained free of bacterial and fungal contamination for thirty days when stored at room temperature (See Table 7).

The initial dose of omeprazole solution was 40 mg, followed by a second 40 mg dose six to eight hours later, then a 20 mg daily dose administered at 8:00 AM. Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5–10 ml of tap water and clamped for at least one hour. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube was removed and the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures: The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-minute lavage or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, Calif.) positive coffee ground material for four consecutive hours that did not clear with lavage (at least 100 ml) and produced a 5% decrease in hematocrit.

Secondary Outcome Measures: The secondary efficacy measures were gastric pH measured four hours after omeprazole was administered, mean gastric pH after starting omeprazole and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, N.Y.) was used to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of one pH unit. Gastric pH was measured before the initiation of omeprazole solution therapy, immediately before each dose, and every four hours between doses.

Other secondary outcome measures were incidence of adverse events (including drug interactions) and pneumonia. Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Prevention and Control definition of nosocomial pneumonia (Garner et al., 1988). According to these criteria, a patient who has pneumonia is one who has rates or dullness to percussion on physical examination of the chest or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and has at least two of the following present: new purulent sputum or changes in character of the sputum, an organism isolated from blood culture, fever or leukocytosis, or evidence of infection from a protective specimen brush or bronchoalveolar lavage. Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia incidence figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present prior to the start of omeprazole suspension.

Cost of Care Analysis: A pharmacoeconomic evaluation of stress ulcer prophylaxis using omeprazole solution was performed. The evaluation included total drug cost (acquisition and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental

confusion), costs associated with clinically significant upper gastrointestinal bleeding. Total drug cost was calculated by adding the average institutional costs of omeprazole 20 mg capsules, 50 ml sodium bicarbonate vials, and 10 ml syringes with needle; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

Statistical Analysis: The paired t-test (two-tailed) was used to compare gastric pH before and after omeprazole solution administration and to compare gastric pH before omeprazole solution administration with the mean and lowest gastric pH value measured after beginning omeprazole.

Results:

Seventy-seven patients met the inclusion and exclusion criteria and received omeprazole solution (See FIG. 2). Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down prior to the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above six as soon as the patient was given a dose of omeprazole solution (in which the enteric coated pellets of omeprazole had been allowed to completely breakdown).

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained above four in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared failures, their pH values were no longer followed.

The ages of the remaining seventy-five patients ranged from eighteen to eighty-seven years; forty-two patients were male and thirty-three were female. All patients were mechanically ventilated during the study. Table 4 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was two to ten, with a mean of 3 (±1) (standard deviation). Five patients enrolled in the study had developed clinically significant bleeding while receiving continuous infusions of ranitidine (150 mg/24 hr) or cimetidine (900 mg/24 hr). In all five cases, the bleeding subsided and the gastric pH rose to above five within thirty-six hours after initiating omeprazole therapy. Three patients were enrolled after having developed two consecutive gastric pH values below three while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH rose to above five within four hours after omeprazole therapy was initiated. Four other patients were enrolled in this study after experiencing confusion (n=2) or thrombocytopenia (n=2) during H_2-antigens therapy. Within thirty-six hours of switching therapy, these adverse events resolved.

Stress-related Mucosal Bleeding and Mortality: None of the sixty-five patients who received buffered omeprazole solution as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only (Gastroccult-positive) within eighteen hours of starting omeprazole solution; bleeding stopped in all patients within thirty-six hours. The overall mortality rate in this group of critically ill patients was eleven percent. No death was attributable to upper gastrointestinal bleeding or the use of omeprazole solution.

Gastric pH: The mean (±standard deviation) pre-omeprazole gastric pH was 3.5±1.9. Within four hours of omeprazole administration, the gastric pH rose to 7.1±1.1 (See FIG. 3); this difference was significant (p<0.001). The differences between pre-omeprazole gastric pH and the mean and lowest gastric pH measurements during omeprazole administration (6.8±0.6 and 5.6±1.3, respectively) were also statistically significant (p<0.001).

Safety: Omeprazole solution was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have been drug-related thrombocytopenia. However, the platelet count continued to fall after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus was unable to continue on omeprazole. No clinically significant drug interactions with omeprazole were noted during the study period. As stated above, metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in omeprazole solution was small (12 mEq/10 ml) and no electrolyte abnormalities were found.

Pneumonia: Pneumonia developed in nine (12%) patients receiving omeprazole solution. Pneumonia was present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic evaluation: The average length of treatment was nine days. The cost of care data are listed in Tables 5 and 6. The costs of drug acquisition, preparation, and delivery for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 5. There were no costs to add from toxicity associated with omeprazole solution. Since two of seventy-five patients required 40 mg of omeprazole solution daily to adequately control gastric pH, the acquisition/preparation cost should reflect this. The additional 20 mg of omeprazole with vehicle adds seven cents per day to the cost of care. Therefore, the daily cost of care for omeprazole solution in the prophylaxis of stress-related mucosal bleeding was $12.60 (See Table 6).

Omeprazole solution is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has been challenged recently. All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage—mechanical ventilation. Previous trials and data from a recently published study show that stress ulcer prophylaxis is of proven benefit in patients at risk and, therefore, it was thought to be unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during omeprazole solution therapy. Gastric pH was maintained above 4 on omeprazole 20 mg/day in seventy-three of seventy-five patients. No adverse events or drug interaction associated with omeprazole were encountered.

TABLE 4

Mech Vent	Major Surgery	Multitrauma	Head Injury	Hypotension	Renal Failure	Sepsis	Multiple Operation	Acid/ Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2
Mech Vent	Major Surgery	Multitrauma	Head Injury	Hypotension	Renal Failure	Sepsis	Multiple Operation	Acid/ Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2

Risk factors present in patients in this study (n = 75)

TABLE 5

		Per day
RANTIDINE (day 1-9)		
Rantidine	150 mg/24 hr	6.15
Ancillary Product (1)	Piggyback (60%)	0.75
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	0.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs x 50%)	14.50
TOTAL for 9 days		304.20
RANTIDINE Cost per day		33.80
CIMETIDINE (day 1-9)		
Cimetidine	900 mg/24 hr	3.96
Ancillary Product (1)	Piggyback	1.25
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	0.40
Sterile Prep required	yes	8.00
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs x 50%)	14.50
TOTAL for 9 days		288.99
CIMETIDINE Cost per day		32.11
SUCRALFATE (day 1-9)		
Sucralfate	1 g x 4	2.40
Ancillary Product (1)	syringe	0.20
Sterile Prep required	no	
R.N. time ($24/hr)	30 minutes/day (includes pH monitoring)	12.00
TOTAL for 9 days		131.40
SUCRALFATE Cost per day		14.60

Note:
Does not include the cost of failure and/or adverse effect.
Acquisition, preparation and delivery costs of traditional agents.

TABLE 6

The average length of treatment was 9 days. Cost of care was calculated from these date

		Per Day	Total
OMEPRAZOLE (day 1)			
Product acquisition cost	40 mg load x 2 (5.66/dose)	11.32	11.32
Ancillary product	materials for solution preparation	0.41	0.41
Ancillary product	syringe w/needle	0.20	0.40
Sterile preparation required	no		
	6 minutes	2.40	4.80
SOS preparation time (R.N.)	21 minutes/day (includes pH monitoring)	8.40	8.40
R.N. time ($24/hr)			

TABLE 6-continued

The average length of treatment was 9 days. Cost of care was calculated from these date

		Per Day	Total
OMEPRAZOLE (days 2-9)			
Product acqusition cost	20 mg per day	2.80	22.65
Ancillary product	materials for solution preparation	0.41	0.82
Ancillary product	syringe w/needle	0.20	1.60
Sterile preparation required	no		
	6 minutes	2.40	4.80
SOS preparation time (R.N.)	18 minutes/day (includes pH monitoring)	8.40	57.60
R.N. time ($24/hr)			
2/75 patient require 40 mg simplified omeparzole solution per day (days 2-9)			
No additional cost for adverse effects or for failure			
TOTAL			
Simplified Omerprazole Solution cost per day			

Pharmacoeconomic evaluation of omeprazole cost of care

TABLE 7

	Time					
	Control	1 hour	24 hour	2 day	7 day	14 day
Conc (mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

Stability of Simplified Omeprazole Solution at room temperature (25° C.)
Values are the mean of three samples

Example X

Bacteriostatic and Fungistatic Effects of Omeprazole Solution

The antimicrobial or bacteriostatic effects of the omeprazole solution were analyzed by applicant. An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made according to the present invention was stored at room temperature for four weeks and then was analyzed for fungal and bacterial growth. Following four weeks of storage at room temperature, no bacterial or fungal growth was detected.

An omeprazole solution (2 mg/ml of 8.4% sodium bicarbonate) made in accordance with the present invention was stored at room temperature for twelve weeks and then was analyzed for fungal and bacterial growth. After twelve weeks of incubation at room temperature, no fungal or bacterial growth was detected.

The results of these experiments illustrate the bacteriostatic and fungistatic characteristics of the omeprazole solution of the present invention.

Example XI

A. Bioequivalency Study.

Healthy male and female study participants over the age of 18 will be randomized to receive omeprazole in the following forms:

(A) 20 mg of a liquid formulation of approximately 20 mg omeprazole in 4.8 mEq sodium bicarbonate qs to 10 ml with water;

(B) 20 mg of a liquid formulation of approximately 2 mg omeprazole per 1 ml of 8.4% sodium bicarbonate.

(C) Prilosec® (omeprazole) 20 mg capsule;

(D) Capsule prepared by inserting non-enteric coated omeprazole 20 mg into a #4 empty gelatin capsule (Lilly) uniformly dispersed in 240 mg of sodium bicarbonate powder USP to form an inner capsule. The inner capsule is then inserted into a #00 empty gelatin capsule (Lilly) together with a homogeneous mixture of 600 mg sodium bicarbonate USP and 110 mg pregelatinized starch NF.

After appropriate screening and consent, healthy volunteers will be randomized to receive one of the following four regimens as randomly assigned by Latin Square. Each subject will be crossed to each regimen according to the randomization sequence until all subjects have received all four regimens (with one week separating each regimen).

Regimen A (20 mg omeprazole in 4.8 mEq sodium bicarbonate in 10 ml volume); Regimen B (20 mg omeprazole in 10 ml 8.4% sodium bicarbonate in 10 ml volume); Regimen C (an intact 20 mg omeprazole capsule); Regimen D (Capsule in capsule formulation, see above). For each dose/week, subjects will have an i.v. saline lock placed for blood sampling. For each regimen, blood samples will be taken over 24 hours a total of 16 times (with the last two specimens obtained 12 hours and 24 hours after drug administration).

B. Patient Eligibility

Four healthy females and four healthy males will be consented for the study.

C. Inclusion Criteria

Signed informed consent.

D. Exclusion Criteria

1. Currently taking H_2-receptor antagonist, antacid, or sucralfate.
2. Recent (within 7 days) therapy with lansoprazole, omeprazole, or other proton pump inhibitor.
3. Recent (within 7 days) therapy with warfarin.
4. History of variceal bleeding.
5. History of peptic ulcer disease or currently active G.I. bleed.
6. History of vagotomy or pyloroplasty.
7. Patient has received an investigational drug within 30 days.
8. Treatment with ketoconazole or itraconazole.
9. Patient has an allergy to omeprazole.

E. Pharmocokinetic Evaluation and Statistical Analysis

Blood samples will be centrifuged within 2 hours of collection and the plasma will then separated and frozen at −10° C. (or lower) until assayed. Pharmacokinetic variables will include: time to peak concentration, mean peak concentration, AUC (0-t) and (0-infinity). Analysis of variance will be used to detect statistical difference. Bioavailability will be assessed by the 90% confidence interval of the two one-sided tests on the natural logarithm of AUC.

F. HPLC Analysis

Omeprazole and internal standard (H168/24) will be used. Omeprazole and internal standard will be measured by modification of the procedure described by Amantea and Narang. (Amantea Mass., Narang PK. *Improved Procedure for Quantification of Omeprazole and Metabolites Using Reversed-Phased High Performance Liquid Chromotography.* J. CHROMATOGRAPHY 426; 216–222 (1988)). Briefly, 20 ul of omeprazole 2 mg/ml $NaHCO_3$ or Choco-Base omeprazole suspension and 100 ul of the internal standard are vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml of dichloroethane, 5 ml of hexane, and 980 ul of sterile water. After the sample is centrifuged, the organic layer is extracted and dried over a nitrogen stream. Each pellet is reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul is injected onto a C_{18} 5 U column equilibrated with the same mobile phase at 1.1 ml/min. Under these conditions, omeprazole is eluted at approximately 5 minutes, and the internal standard at approximately 7.5 minutes. The standard curve is linear over the concentration range 0–3 mg/ml (in previous work with SOS), and the between-day coefficient of variation has been <8% at all concentrations. The typical mean R^2 for the standard curve has been 0.98 in prior work with SOS (omeprazole 2 mg/ml $NaHCO_3$ 8.4%).

Applicant expects that the above experiments will demonstrate there is more rapid absorption of formulations (a), (b) and (d) as compared to the enteric coated granules of formulation (c). Additionally, applicant expects that although there will be a difference in the rates of absorption among forms (a) through (d), the extent of absorption (as measured by the area under the curve (AUC)) should be similar among the formulations (a) through (d).

Example XII

Intraveneous Proton Pump Inhibitor in Combination With Oral Parietal Cell Activator

Sixteen (16) normal, healthy male and female study subjects over the age of 18 will be randomized to receive pantoprazole as follows:

(a) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of sodium bicarbonate 8.4%; and

(b) 40 mg IV over 15 to 30 minutes in combination with a 20 ml oral dose of water.

The subjects will receive a single dose of (a) or (b) above, and will be crossed-over to (a) and (b) in random fashion. Serum concentrations of pantoprazole versus time after administration data will be collected, as well as gastric pH control as measured with an indwelling pH probe.

Further, similar studies are contemplated wherein chocolate or other parietal cell activator is substituted for the parietal cell activator sodium bicarbonate, and other proton pump inhibiting agents are substituted for pantoprazole. The parietal cell activator can be administered either within about 5 minutes before, during or within about 5 minutes after the IV dose of proton pump inhibitor.

Applicant expects that these studies will demonstrate that significantly less IV proton pump inhibitor is required to achieve therapeutic effect when it is given in combination with an oral parietal cell activator.

Additionally, administration kits of IV proton pump inhibitor and oral parietal cell activator can be packaged in many various forms for ease of administration and to optimize packing and shipping the product. Such kits can be in unit dose or multiple dose form.

Example XIII

Six (6) Month Stability of Omeprazole Suspension.

A suspension was prepared by mixing 8.4% sodium bicarbonate with omeprazole to produce a final concentra-

tion of 2 mg/ml to determine the stability of omeprazole solution after 6 months. The resultant preparation was stored in clear glass at room temperature, refrigerated and frozen. Samples were drawn after thorough agitation from the stored preparations at the prescribed times. The samples were then stored at 70° C. Frozen samples remained frozen until they were analyzed. When the collection process was completed, the samples were shipped to a laboratory overnight on dry ice for analysis. Samples were agitated for 30 seconds and sample aliquots were analyzed by HPLC in triplicate according to well known methods. Omeprazole and the internal standard were measured by a modification of the procedure described by Amantea and Narang. (Amantea Mass., Narang PK, *Improved Procedure For Quantitation Of Omeprazole And Metabolites Using Reverse-Phased High-Performance Liquid Chromatography*, J. CHROMATOGRAPHY, 426:216–222 (1988)). Twenty (20) ul of the omeprazole 2 mg/ml $NaHCO_3$ solution and 100 ul of the internal standard solution were vortexed with 150 ul of carbonate buffer (pH=9.8), 5 ml dichloroethane, 5 ml hexane, and 980 ul of sterile water. The sample was centrifuged and the organic layer was extracted and dried over a nitrogen stream. Each pellet was reconstituted with 150 ul of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 ul were injected onto a C185u column equilibrated with the same mobile phase at 1.1 ml/min. Omeprazole was eluted at ~5 min, and the internal standard at ~7.5 min. The standard curve was linear over the concentrated range 0–3 mg/ml, and between-day coefficient of variation was <8% at all concentrations. Mean R^2 for the standard curve was 0.980.

The 6 month sample showed stability at greater than 90% of the original concentration of 2 mg/ml. (i.e., 1.88 mg/ml, 1.94 mg/ml, 1.92 mg/ml).

Example XIV

Pharmacokinetic and Pharmacodynamic Study of Duodenal or Jejunal Administration Compared to Nasogastric Administration of Omeprazole Suspension in Patients at Risk for Stress Ulcers

Omeprazole suspension administered by the jejunal or duodenal route was compared in a randomized, cross-over fashion with nasogastric administration in patients at risk for stress-related GI bleeding. Eligible for study enrollment were all adult patients (>18 yr.) admitted to the surgical intensive care unit who had recently undergone a major surgical procedure or were posttrauma with an Acute Physiological and Chronic Health Evaluation (APACHE II) score >18. To be included in the study, patients were also required to be mechanically ventilated in addition to having at least one of the following risk factors: head injury with altered level of consciousness; extensive burns (>20% body surface area); acute renal failure; acid-base disorder; multiple traumas; coagulopathy; multiple operative procedures; coma; hypotension for >1 h; or sepsis syndrome. Patients were excluded from participation if they had any of the following characteristics: hypochlorhydria; status of "Do Not Resuscitate"; a history of vagotomy, pyloroplasty, or gastroplasty; an allergy to proton pump inhibitors; active GI bleeding (including variceal bleeding); thrombocytopenia (<30,000/mm^3 platelets); active peptic ulcer disease treated within the past year; were likely at risk of swallowing blood (i.e., severe facial trauma, oral lacerations, hemoptysis); currently or during the study receiving ketoconazole or itraconazole or enteral tube feedings; or had received an investigational drug within 30 days, omeprazole or another proton pump inhibitor within 5 days, or warfarin or nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, within 24 h. Administration of the study drug was not initiated until the patient had documented gastric pH of <4.0. If 48 h had passed and gastric pH was not <4.0, the patient was excluded from study participation. Patients who were on prior acid reducing therapy for <24 h were allowed to participate after discontinuation of their medication and gastric acidity achieved the study-imposed pH range (gastric pH<4.0). Subjects were not allowed to receive antisecretory agents (e.g., H2RA) during the study. The institutional Review Board for the University of Missouri at Columbia approved the protocol and informed consent was obtained before study enrollment for every subject.

Omeprazole suspension was compounded and stored in amber bottles at 4° C. The omeprazole was prepared by dissolving the contents of two 20-mg capsules (Prilosec®), Astra-Zeneca, Wayne, Pa.) in 20 ml of 8.4% sodium bicarbonate (Abbott Laboratories, North Chicago, Ill.) with gentle shaking to assure adequate mixing. The sodium bicarbonate dissolves the enteric-coated beads leaving "free omeprazole" in the suspension.

A nasogastric tube and needle catheter jejunostomy or duodenal tube was placed before study initiation. Placement of the nasogastric tube was confirmed by x-ray and aspiration of gastric contents for pH confirmation. The jejunostomy and duodenal tubes were placed by standard surgical technique and positioning was confirmed by x-ray. On study day 1, when gastric pH decreased to <4, the patients were randomized to receive a single 40 mg dose of omeprazole suspension by either nasogastric tube or jejunal/duodenal administration. When gastric pH subsequently dropped again to <4 (>24 h in all patients), each patient was crossed-over to the other administration route followed by a single 40 mg dose of omeprazole suspension. All patients received the cross-over dose 72 h after the first day and after the pH had dropped to <4. After omeprazole administration, the nasogastric or duodenal/jejunal tube was flushed with 10 ml of water and clamped for 1–2 h. A Latin square cross-over design was used.

A total of 60 ml of blood was collected in 2.5 ml aliquots over a period of 24 h to establish the absorption and pharmacokinetic parameters of omeprazole as administered by the different enteral routes. Blood samples were obtained immediately before each dose of drug and at 3, 5, 10, 20, 30, 60, 120, 240, 480, 720, 960, and 1440 min after drug administration. All samples were collected in red-top tubes (Vacutainer®, Becton-Dickinson, Franklin Lakes, N.J.), allowed to clot for 30 min at room temperature, and centrifuged for 10 minutes at 1000 g. The resulting sera was removed and immediately frozen at −70° C. until analysis. The study was conducted for approximately 4 days per patient.

Continuous monitoring of gastric acidity (pH) occurred throughout the study period for all patients who received omeprazole suspension. Continuous gastric pH readings were measured with a Zinetics probe (Zinetics Medical, Salt Lake City, Utah).

Omeprazole plasma concentrations were determined by modification of a previously published high-performance liquid chromatography assay. The range of linearity for the assay was 25–1000 ng/ml for serum. The lower limits of detection were 10 ng/ml. Coefficients of variation (R^2) for the omeprazole assay over the standard curve concentrations were >0.99 for the entire study. Intra- and interassay coefficients of variation were consistently <8.5% at concentrations included in the linearity range.

The serum omeprazole concentration-time data were analyzed via WinNonlin Software, Standard Edition, Version

1.5 (Scientific Consulting, Cary, N.C.). First dose pharmacokinetic parameters including half-life ($T_{1/2}$), maximum serum-concentration (C_{max}), time to maximum serum concentration (T_{max}), drug clearance (Cl_{ss}/F) were estimated using a noncompartmental extravascular dose model. Area under the serum-concentration time curve (AUC) was determined by trapezoidal rule and was extrapolated to 24 h (AUC_{0-24}) and to infinity ($AUC_{0-\infty}$), using the fitted values of the final plasma concentration time curves.

Demographic, pH, and pharmacokinetic data are reported as the mean±SD as well as the range for respective values when appropriate. The pharmacodynamic relationship between various pharmacokinetic parameters, including clearance (Cl and AUC, were compared to mean pH values obtained for each respective administration route and analyzed by linear regression. Omeprazole concentrations-time data, graphical representation, and statistical analysis were performed with Prism software (GraphPad, Chicago, Ill.). A p value of <0.05 was considered significant for all statistical analyses.

Omeprazole absorption and pharmacokinetic analyses were performed in nine critically ill surgical patients (five men and four women). The administration was well tolerated without any apparent adverse events. The mean (±SD) age, weight, and creatinine clearance of these patients were 33±11 yr (range, 23–56 yr), 78±19 kg (range, 59–124 kg), and 95±24.0 ml/min (range, 35–120 ml/min), respectively. No patients had demonstrated liver disease by either clinical or laboratory evidence of hepatic dysfunction. All nine patients received omeprazole via nasogastric administration, compared with seven and two patients who were also randomized to receive the drug via the jejunal or duodenal route, respectively. Pharmacokinetic parameters for both groups are shown in Table 8. The mean plasma concentration-time curves after 40 mg of omeprazole suspension administered via the nasogastric and jejunal/duodenal routes produced a biphasic curve with the higher peak serum concentrations resulting from the jejunal/duodenal group compared to nasogastric administration (1.833±0.416 μg/m vs. 0.970±0.436 μg/ml, p=0.006). Omeprazole absorption was also significantly slower by comparison of time to maximum concentration (T_{max}) when administered by nasogastric tube vs. jejunal/duodenal administration (108.3±42.0 vs. 12.1±7.9 min. p<0.0001). Other mean pharmacokinetic parameters ($t_{1/2}$, Cl_{ss}, AUC_{0-24}, $AUC_{0-\infty}$) were not statistically different between the two groups, although there was a trend toward a shorter half-life for patients who received drug via the jejunal/duodenal route.

The mean baseline pH was 1.63±0.89 for the jejunal/duodenal group and 2.12±0.67 for the nasogastric group (p=0.26). Mean intragastric pH values rose to >4 1 h after omeprazole administration and remained >4 for the entire 24-h study period in both groups. When comparing the mean pH data (nasogastric (6.32±1.04) vs. jejunal/duodenal (5.57±1.15), p=0.015) nasogastric administration maintained higher gastric pH values throughout the study with fewer incidences of pH values <4.0 overall.

TABLE 8

Pharmacokinetic Parameters of Omeprazole Suspension

Variable	Nasogastric (N = 9)	Jejunal/Duodenal (N = 9)	p Value
AUC_{0-24}	373.3 ± 256.2	375.3 ± 340.1	0.99
$AUC_{0-\infty}$	415.1 ± 291.8	396.7 ± 388.1	0.91
T_{max} (min)	108.3 ± 42.0	12.1 ± 7.9	<0.001
$T_{1/2}$ (min)	250.7 ± 100.0	162.9 ± 138.9	0.14

TABLE 8-continued

Pharmacokinetic Parameters of Omeprazole Suspension

Variable	Nasogastric (N = 9)	Jejunal/Duodenal (N = 9)	p Value
Cl/F	0.144 ± 0.098	0.199 ± 0.137	0.34
C_{max} (μg/ml)	0.970 ± 0.436	1.833 ± 0.416	0.0006

Data expressed as mean ± SD.
p < 0.05 considered statistically significant.
AUC_{0-24} = area under the curve from 0 to 24 h;
$AUC_{0-\infty}$ = Area under the curve from 0 h to infinity;
T_{max} = time to maximum serum concentration;
$T_{1/2}$ = half life;
Cl/F = drug clearance;
C_{max} = maximum serum concentration.

In summary, nasogastric administration of SOS resulted in lower maximum mean±SD serum concentrations compared to jejunal/duodenal dosing (0.970±0.436 vs. 1.833±0.416 μg/ml, p=0.006). SOS absorption was significantly slower when administered via nasogastric tube (108.3±42.0 vs. 12.1±7.9 min,p<0.001). However, all routes of administration resulted in similar SOS area under the serum concentration-time curves ($AUC_{0-\infty}$) (415.1±291.8 vs. 396.7±388.1 μg h/ml, p=0.91). Mean intragastric pH values remained >4 at 1 h after SOS administration and remained >4 for the entire 24-h study (nasogastric (6.32±1.04) vs. jejunal/duodenal (5.57±1.15), p=0.015), regardless of administration route.

Example XV

Simplified Omeprazole Suspension (SOS) Pharmacokinetic/pharmacodynamic Study in Patients at Risk for Stress-related Mucosal Damage (SRMD).

A. Protocol

Hospitalized patients who were at risk of stress-related mucosal damage (SRMD) were enrolled in this study to evaluate the serum concentration vs. time profile and intragastric pH changes accompanying a single dose of omeprazole 40 mg in 20 mEq sodium bicarbonate suspension. Patients at risk for SRMD were considered eligible and received no prior treatment with omeprazole (within 5 days). Informed Consent was obtained. A nasogastric tube (with a pH probe—incorporated in the tip—GraphProbe ZineticsMedical) was placed in the stomach by standard means. Patients received a dose of SOS (40 mg omeprazole in 20 mL 8.4% sodium bicarbonate) after the gastric pH dropped below 4. Serum concentrations of omeprazole were drawn at the following times:

0 min	3 min	5 min	10 min	15 min	20 min
30 min	45 min	1 hr	2 hrs	4 hrs	8 hrs
12 hrs	24 hrs				

Gastric pH tracings were made using the ZineticsMedical GraphProbe and the DataLogger from Sandhill scientific.

Serum was ultracentrifuged and stored at −70° C. and sent as a single batch to David Flockhart Md., PhD at Georgetown University Medical Center for HPLC (High Pressure Liquid Chromatography) measurement.

B. Results

The omeprazole plasma concentrations for 17 subjects are provided below in Table Nos. 12, 13, 14, and 15. Below is also a summary the pharmacokinetic and pharmacodynamic findings.

1. Phlarmacokinetic

Absorption: Absorption was rapid as indicated by the appearance of omeprazole in serum at <10 minutes in many subjects.

Tmax: The C max (maximum serum concentration) was also rapidly attained when compared to the enteric-coated granules. The C max in most every patient appearing before 1 hour (Tmax).

AUC: The absorption of the omeprazole did not appear to be significantly decreased when compared to omeprazole in the enteric-coated form as measured by Area Under the Curve (AUC).

2. Pharmacodynamic

The gastric pH control appeared to be very rapid and sustained at an unusually high pH for a first dose of omeprazole.

TABLE 9

Omeprazole Concentrations Over time for Patient Nos. 1-5 (μg/ml)

Time	Patient #1 [Omeprazole] μg/ml plasma	Patient #2 [Omeprazole] μg/ml plasma	Patient #3 [Omeprazole] μg/ml plasma	Patient #4 [Omeprazole] μg/ml plasma	Patient #5 [Omeprazole] μg/ml plasma
1 min.	ND	ND	ND	ND	ND
3 min.	ND	0.155	0.149	0.02	ND
5 min.	0.201	0.44	0.165	0.148	0.1
10 min.	0.322	0.551	0.233	0.34	0.278
15 min.	ND	0.587	0.261	0.44	0.413
20 min.	0.381	1.01	0.382	0.554	0.537
30 min.	0.445	1.33	0.386	0.718	0.628
45 min.	0.658	1.46	0.445	0.89	0.68
1 hr.	0.755	1.24	0.501	0.893	0.749
2 hrs.	0.911	0.894	0.715	0.695	0.763
4 hrs.	0.976	0.13	0.463	ND	0.622
8 hrs.	0.78	0.05	0.305	ND	0.319
12 hrs.	0.303	ND	0.293	ND	0.133
18 hrs.	ND	ND	ND	ND	ND
24 hrs.	0.218	ND	0.215	ND	ND

TABLE 10

Omeprazole Concentrations Over time for Patient Nos. 6–10 (μg/ml)

Time	Patient #6 [Omeprazole] μg/ml plasma	Patient #7 [Omeprazole] μg/ml plasma	Patient #8 [Omeprazole] μg/ml plasma	Patient #9 [Omeprazole] μg/ml plasma	Patient #10 [Omeprazole] μg/ml plasma
1 min.	ND	ND	ND	ND	ND
3 min.	ND	ND	ND	ND	0.041
5 min.	ND	0.756	0.291	0.044	0.058
10 min.	0.067	1.15	0.316	0.0525	0.117
15 min.	0.072	0.95	0.34	0.073	0.192
20 min.	0.05	ND	0.44	0.096	0.213
30 min.	0.0925	ND	0.66	0.152	0.237
45 min.	0.095	ND	0.437	0.186	0.234
1 hr.	0.058	0.623	0.386	0.24	0.263
1 hr. 15 min.	ND	0.61	ND	ND	ND
2 hrs.	0.012	0.177	0.153	0.406	0.221
4 hrs.	ND	0.107	0.044	0.865	0.391
8 hrs.	ND	ND	ND	0.303	0.164
12 hrs.	ND	ND	ND	0.168	0.055
18 hrs.	ND	ND	ND	ND	ND
24 hrs.	ND	ND	ND	0.108	ND

TABLE 11

Omeprazole Concentrations Over time for Patient Nos. 11–15 (μg/ml)

Time	Patient #11 [Omeprazole] μg/ml plasma	Patient #12 [Omeprazole] μg/ml plasma	Patient #13 [Omeprazole] μg/ml plasma	Patient #14 [Omeprazole] μg/ml plasma	Patient #15 [Omeprazole] μg/ml plasma
1 min.	ND	ND	ND	ND	ND
3 min.	0.0275	ND	ND	ND	ND
5 min.	0.0735	ND	ND	ND	0.1075 (or 20 min.)
10 min.	0.131	ND	1.12	0.131	0.155
15 min.	0.154	ND	1.08	0.161	0.176
17 min.	ND	ND	ND	ND	ND

TABLE 11-continued

Omeprazole Concentrations Over time for Patient Nos. 11–15 (μg/ml)					
Time	Patient #11 [Omeprazole] μg/ml plasma	Patient #12 [Omeprazole] μg/ml plasma	Patient #13 [Omeprazole] μg/ml plasma	Patient #14 [Omeprazole] μg/ml plasma	Patient #15 [Omeprazole] μg/ml plasma
20 min.	0.177	0.012	1.04	0.187	ND (or 5 min.)
30 min.	0.388	0.025	0.865	0.224	0.184
45 min.	0.526	0.046	0.841	0.269	0.196
1 hr.	0.486	0.077	0.896	0.276	0.155
2 hrs.	0.458	0.128	0.504	0.343	0.17
4 hrs.	0.466	0.17	0.278	0.435	0.139
8 hrs.	0.232	0.148	0.145	0.204	ND
12 hrs.	0.093	0.052	ND	0.131	ND
18 hrs.	ND	ND	ND	ND	ND
24 hrs.	ND	ND	ND	ND	ND

TABLE 12

Omeprazole Concentrations Over time for Patient Nos. 16–17 (μg/ml)		
Time	Patient #16 [Omeprazole] μg/ml plasma	Patient #17 [Omeprazole] μg/ml plasma
1 min.	ND	ND
3 min.	ND	ND
5 min.	ND	ND
10 min.	ND	0.504
15 min.	ND	0.6932
20 min.	ND	0.765
30 min.	0.076	0.777
45 min.	0.186	0.645
1 hr.	0.242	0.547
2 hrs.	0.193	0.508
4 hrs.	ND	ND
8 hrs.	ND	ND
12 hrs.	ND	ND
18 hrs.	ND	ND
24 hrs.	ND	ND

Example XVI

A Comparison of the Pharmacokinetics and Pharmacodynamics of Omeprazole Delivered Orally with Different Doses of Antacid in Fasted Subjects

A. Administration of Test Articles

Test articles were administered to each subject according to the following schedule:

Period 1:1 antacid tablet (30 mEq of 1 part sodium bicarbonate to 3 parts calcium carbonate) plus 40 mg omeprazole powder was administered in the fasted state with 60 mL (2 oz.) water.

Period 2: A solution/suspension of omeprazole 40 mg and 20 mEq of sodium bicarbonate (total volume 20 mL in an amber bottle) was administered to the subject. Immediately (within 30 seconds) after administration, the bottle was rinsed with a small amount of water, which was also administered to the subject. The rinse step was repeated and the subject was given a total of 100 mL of water after the administration of the 20 mL of the omeprazole/sodium bicarbonate solution/suspension.

Period 3:1 capsule of Prilosec (40 mg of enteric-coated omeprazole alone) in the fasted state with 120 mL water.

Period 5:1 antacid tablet (30 mEq of 1 part sodium bicarbonate to 1 part calcium carbonate) plus 40 mg omeprazole powder was administered in the fasted state with 120 ml water.

B. Treatment Periods

Only 1 day (Day 1) was required in the clinic. Subjects fasted for at least 10 hours overnight in the clinic prior to initiating pH monitoring; they were allowed water ad libitum until 1 hour prior to dose administration.

Each subject receiving 40 mg of omeprazole powder was administered the drug product by site staff directly onto the dorsal mid-tongue. Immediately thereafter, subjects were administered one or two chewable antacid tablets and began chewing. Each subject continued to chew the tablet(s), while mixing it with the omeprazole powder, carefully avoiding swallowing the powder immediately. One minute after initiating chewing (and after completely swallowing the test articles), each subject drank 60–120 mL of water rising the oral cavity before swallowing. No additional water was allowed until after the 6-hour postdose pH and blood samples were taken. Water was allowed ad libitum. For pharmacokinetic/pharmacodynamic sampling, zero time was the time that chewing is initiated.

C. Inclusion Criteria

Subjects were included in the trial if they met all of the following:

1. Were non-Asian males from 18 to 45 years of age.
2. Were within the ranges of about 20% of ideal body weight.
3. Were in good health on the basis of history, physical examination, and laboratory values.
4. Had not used any form of tobacco (e.g., smoking, chewing) for the last year.
5. Tolerated installation of nasogastric pH probe for at least 5 minutes.
6. Had a basal gastric pH at each trial visit of less than 2.5.

D. Exclusion Criteria

Subjects were excluded from the trial if they met any of the following:

1. Had a significant history odor concurrent gastrointestinal disease or condition, such as GERD, heartburn, reflux esophagitis, peptic ulcer disease (gastric or duodenal), or a family history of peptic ulcer disease, gastric surgery (e.g., vagotomy, pyloroplasty).
2. Had any significant medical history or concurrent illness, such as respiratory, allergic, psychiatric, neurological, renal, hepatic, cardiovascular, metabolic, or endocrine condition, or any other medical condition which the investigator or medical monitor considered sufficiently serious to interfere with the conduct, completion, or results of the trial, or constituted an unacceptable risk to the subject.
3. Had a history of significant drug allergy.
4. Known hypersensitivity to any of the ingredients in the test articles.

5. Had a positive urine test of alcohol or other drugs at any trial visit.
6. Had taken any gastric antisecretory drugs, e.g., H2 antagonists or PPIs, or antacids (including OTC medications) within 14 days prior to Period 1 or during the trial.
7. Had taken xanthine-containing foods or beverages (e.g., coffee, tea, chocolate) within 48 hours of entering the clinic for each trial period.
8. Had ingested grapefruit juice within 7 days of dose administration in any trial period.
9. Had donated blood within 90 days of entering the trial.
10. Had been treated with any investigational drug or therapy, or participated in a clinical trial in the 90 days prior to entering the trial.
11. Had any condition which could have interferes with assessments, posed additional risks in administration of the trial drug to the subject, or precluded completion of the trial, including a history of noncompliance, alcoholism, or drug abuse.
12. Had any laboratory test results deviating from the normal reference ranges established by the local laboratory by more then 20% that the investigator judged to be of possible clinical significance.
13. Evidence of infection with HIV.
14. Known carrier of hepatitis B surface antigen.
15. Known carrier of hepatitis C antibody.

E. Omeprazole Pharmacokinetics

Blood samples (10 mL) for measurement of plasma omeprazole were taken within 30 minutes prior to each dosing, and at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, and 360 minutes (6 hours) after dosing. These samples were taken at the same time as the gastric pH was being recorded. Plasma omeprazole was measured using a previously validated LC-MSMS assay. Zero time was the time that the subject first chewed a table formulation, swallowed a capsule, or first swallowed a liquid formulation of test article.

F. Test Article Evaluation (Day 1)

On Day 1, after a greater than or less than 10 hour fast, pH recordings of the gastric fluid began in the morning for 1 hour prior to dosing. The pH monitoring continued for 6 hours postdose.

G. Pharmacokinetic Analysis of Omeprazole

The following pharmacokinetic parameters were evaluated:

Omeprazole plasma concentration at each sampling time.

Peak omeprazole plasma concentration (C_{max}) and time to peak plasma concentration (T_{max}) obtained directly from the data without interpolation.

Terminal elimination rate constant (k_{el}) determined from a log-linear regression analysis of the terminal plasma omeprazole concentrations.

Terminal elimination half-life ($t_{1/2}$) calculated as $0.693/k_{el}$.

Area under the omeprazole plasma concentration-time curve from time zero to time "t" (AUC_{0-t}), calculated using the trapezodial rule with the plasma concentration at time "t" being the last measurable concentration.

Area under the omeprazole plasma concentration-time curve from time zero to time infinity (AUC_{0-inf}), calculated as $AUC_{0-t}+C_t/k_{el}$, where C_t is the last measurable plasma concentration and k_{el} is the terminal elimination rate constant defined above.

H. Onset, Duration, and Magnitude of Effects

On set of action was defined as the earliest time that the value with active treatment was significantly different from the corresponding baseline value. The baseline value for each subject was the mean of values from the twelve 5-minute baseline periods.

Duration of action was the latest time that the value with active treatment was significantly different from the corresponding baseline value.

Magnitude of effect was evaluated for each 5-minute postdosing interval as well as for the postdosing intervals 0–360 minutes.

I. Description

The chewable antacid tablets were produced by Murty Pharmaceuticals, Inc. (518 Codell Drive, Lexington, Ky. 40509-1016) and contained sodium bicarbonate and calcium carbonate, as well as common excipients. Additional formulation(s) for oral administration and At, may contain sodium bicarbonate and/or calcium carbonate either as a tablet or liquid, in addition to omeprazole. USP grade, bulk omeprazole was purchased from Esteve Quimica, S. A. (Barcelona, Spain).

At the trial site, the pharmacy staff mixed omeprazole powder with powdered peppermint flavoring and Equal® Sweetener (containing aspartame) [1 part omeprazole: 2 parts peppermint flavoring:1.8 part Equal®]. For each unit dose, 120 mg (containing 40 mg omeprazole powder) was weighed on an analytic balance within 1–2 hours of dose administration in each time period. This mixture was stored under controlled conditions of humidity and temperature.

J. Results

The omeprazole plasma concentrations for 10 subjects of the study are provided below in Table No. 13.

TABLE 13

Sub		Omeprazole Concentrations (ng/ml)												
		Sampling Times (hour)												
No.	Period	0.00	0.08	0.17	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00
1	1	0.00	16.4	321	738	968	783	605	357	211	97.9	40.1	16.9	11.4
1	2	0.00	79.3	312	388	441	454	292	200	128	43.4	21.0	9.44	4.32
1	3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	39.4	120	366	406	161	109
1	5	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
2	1	0.00	6.82	234	326	582	875	615	322	220	84.2	38.1	14.7	6.39
2	2	0.00	47.6	84.3	168	1040	717	484	265	162	67.6	26.2	11.6	4.02
2	3	0.00	0.00	0.00	0.00	1.57	51.3	98.6	363	379	429	204	99.0	51.2
2	5	0.00	22.9	315	661	983	797	582	375	306	124	57.8	25.3	12.2
3	1	0.00	203	1230	1450	1000	693	525	306	191	79.3	32.2	14.8	7.22
3	2	0.00	20.6	302	583	831	740	573	336	203	82.0	37.6	17.6	9.38
3	3	0.00	0.00	0.00	0.00	9.85	57.7	179	683	681	345	158	85.4	45.9

TABLE 13-continued

Sub		Omeprazole Concentrations (ng/ml)												
		Sampling Times (hour)												
No.	Period	0.00	0.08	0.17	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00
3	5	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
4	1	0.00	4.57	164	516	1230	780	495	254	153	55.0	20.8	8.52	3.93
4	2	0.00	9.53	61.6	471	881	566	388	182	107	36.5	17.9	6.17	2.63
4	3	0.00	0.00	0.00	0.00	0.00	0.00	18.6	386	454	233	126	81.3	51.7
4	5	0.00	196	1240	1740	994	644	493	305	207	101	44.3	18.9	8.16
5	1	0.00	107	984	1080	662	409	250	118	60.3	19.7	7.44	2.95	1.47
5	2	0.00	385	1400	1380	693	394	278	144	78.1	21.8	7.20	2.16	BQL
5	3	0.00	0.00	0.00	BQL	9.25	44.0	319	340	252	95.5	38.8	14.6	8.16
5	5	0.00	88.9	1210	1120	677	430	325	173	97.8	35.1	13.4	5.04	2.06
6	1	0.00	32.8	349	552	648	425	267	133	68.4	24.7	9.90	4.21	2.72
6	2	0.00	13.0	68.8	101	469	349	241	212	104	31.8	9.31	3.17	1.16
6	3	0.00	0.00	0.00	0.00	24.0	234	588	351	162	85.0	29.0	14.4	5.59
6	5	0.00	5.72	26.6	50.2	190	514	398	177	108	51.3	22.0	7.75	3.45
7	1	0.00	5.24	97.4	269	638	543	431	255	164	63.6	29.0	11.9	5.79
7	2	0.00	84.0	960	1170	899	543	433	231	140	54.1	24.0	12.0	5.54
7	3	0.00	0.00	0.00	5.42	31.0	992	1110	515	310	115	47.0	21.8	9.32
7	5	0.00	5.35	72.9	165	363	302	221	268	256	150	71.1	29.4	11.4
8	1	0.00	49.9	358	746	1090	784	609	367	243	104	51.1	23.1	12.1
8	2	0.00	38.6	262	1280	846	563	434	237	148	66.9	29.5	15.7	6.15
8	3	0.00	0.00	0.00	0.00	0.00	3.84	80.6	401	313	476	225	108	47.1
8	5	0.00	19.7	148	582	1130	822	688	461	264	132	64.5	31.8	15.8
9	1	0.00	16.0	139	309	462	355	330	605	317	111	47.2	21.9	10.2
9	2	0.00	277	1550	1740	1150	744	522	305	178	79.2	36.6	14.1	6.96
9	3	0.00	0.00	0.00	0.00	0.00	1.62	47.7	551	566	287	153	98.0	52.5
9	5	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
10	1	0.00	15.8	130	202	311	233	456	378	187	61.6	21.2	9.90	4.20
10	2	0.00	250	1010	1100	634	421	310	136	80.7	28.5	11.6	4.85	1.87
10	3	0.00	0.00	0.00	0.00	5.80	114	148	366	390	174	79.4	29.2	10.5
10	5	0.00	103	994	1190	702	562	353	198	110	36.7	14.3	5.40	2.28

NS = No Sample
LOQ = Limit of quantitation: 1.00 ng/ml
BQL = Below quantitation limit

VI. Proton pump inhibitor Compositions and Method for Optimizing the Buffer to be Administered in Combination With a Proton Pump Inhibitor

A. Introduction

The compositions of the present invention are designed to produce rapid release of active drug to the site of delivery (typically the stomach) without the necessity of enteric coatings or delayed released dosage forms, while preventing acid degradation of the drug. Acid labile proton pump inhibiting agents, for example, can be formulated or coadministered with one or more buffers sufficient to protect the proton pump inhibitor in any environment, with the ultimate goal being to deliver a proton pump inhibitor to the stomach (or other environment) either via a liquid, a powder or solid dosage form that produces an immediate release of active drug to the site of delivery such that the proton pump inhibitor is quickly available for absorption. Accordingly, Applicant has found that certain amounts of buffers coadministered or mixed with certain proton pump inhibiting agents prevent acid degradation of the proton pump inhibitor when the buffers produce a pH in the stomach or other site of environment that is equal to the pKa of the proton pump inhibitor plus an amount sufficient to protect the proton pump inhibitor from acids and provide undegraded and bioactive proton pump inhibitor to the blood upon administration (e.g., a final pH of pKa of proton pump inhibitor+0.7 log value will reduce the degradation to about 10%). Such buffers should interact with hydrogen ion at rates that exceed the interaction of hydrogen ion with the proton pump inhibitor. Thus, the solubilities of the buffers and proton pump inhibiting agents are important considerations because solubility is a key determinant of the rate of interaction of H+ ion with another compound.

Typically, a proton pump inhibitor formulation of the present invention comprises two primary components: a proton pump inhibitor and an Essential Buffer. An Essential Buffer may include a buffer or combination of buffers that interact with HCl (or other acids in the environment of interest) faster than the proton pump inhibitor interacts with the same acids. When placed in a liquid phase (usually in water), the Essential Buffer produces and maintains a pH of at least the pKa of the proton pump inhibitor. In one embodiment, by raising the pH of the environment to the same of the pKa of the proton pump inhibitor plus about 0.7 log value (or greater), the expected degradation (ionization) can be reduced from about 50% to about 10%. As used herein, the "Essential pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the proton pump inhibitor. The buffering agent(s) employed may raise the pH of the environment to the Essential pH such that 30%, 40% or 50% of the proton pump inhibitor is undegraded, or be present in an amount sufficient to substantially protect (i.e., greater than 50% stability) the proton pump inhibitor.

In another embodiment, the Essential pH is the pKa of the proton pump inhibitor. In a further embodiment, the Essential pH is the sum of the pKa of the proton pump inhibitor plus log 0.7. A log value of about 0.7 is added to the pKa, which represents a decrease of about 5.01187% in stability of the proton pump inhibitor from the pKa plus 1 log value, thus resulting in a stability of approximately 90%, a value widely accepted as desirable in pharmaceutical products. In some cases it may be permissible to accept a value of less than log 0.7.

One aspect of the invention provides that there is also sufficient buffer available to provide the neutralization

capacity (Essential Buffer Capacity ("EBC")) to maintain the elevated pH of the environment (usually gastric) throughout the dwell time that the proton pump inhibitor is passed from the environment and into the blood.

B. Essential Buffers

Essential Buffers can be divided into two groups: Primary Essential Buffers and Secondary Essential Buffers. Every formulation is combined with, either directly or indirectly, at least one Primary Essential Buffer. The Primary Essential Buffers, when used alone or in combination, provide buffering activity below the value that leads to tissue irritation or damage and above a lower limit for the Essential pH of the proton pump inhibitor. Secondary Essential Buffers are not required in every formulation but can be combined with Primary Essential Buffers to produce a higher pH and added neutralization capacity for the formulation.

Determining the type and dose of buffer to protect acid labile substituted benzimidazole proton pump inhibiting agents (and other drugs) is useful for efficacious proton pump inhibitor delivery to and action upon parietal cell proton pumps, particularly when the proton pump inhibitor is administered as an immediate release product designed to disintegrate in the stomach rather than a traditional delayed-release product designed to disintegrate beyond the stomach in higher pH environments such as the duodenum. The present compositions and methods employ determinations of the nature of the buffer(s) to be used, as well as calculations to determine Essential pH, buffering capacity, and volume measurements for individual proton pump inhibitor doses based on their respective solubilities and pKa's. Such inventive methods are applicable for determining the type and amount of buffer(s) necessary to protect the proton pump inhibitor in an array of environments (e.g., mouth, esophagus, stomach, duodenum, jejunum, rectal vault, nasogastric tube, or a powder, tablet, capsule, liquid, etc. in storage before administration). Dosage forms in storage may be exposed to various environments, but a typical set of storage conditions includes storage at room temperature (65–80° F.), and minimal or no exposure to heat, cold, light or humidity as is known in the art.

The present method includes all substituted benzimidazole proton pump inhibiting agents, their salts, esters, amides, enantiomers, racemates, prodrugs, derivatives and the like, and is not limited to those proton pump inhibiting agents used to exemplify the following calculations.

The Essential Buffering Capacity ("EBC") is the capacity of a proton pump inhibitor/buffer formulation to resist degradation from its environment. The buffering capacity of a proton pump inhibitor/buffer formulation is primarily derived from components of the formulation that possess the ability to combine with acids (H+ ions) from the environment. The EBC contributes to both acid neutralization (antacid effect) and to maintaining an environmental pH>pKa+0.7 to protect proton pump inhibiting agents from acid degradation throughout the dwell time. The Primary Essential Buffer is designed to maintain the pH of stomach contents (or other environment) at a somewhat constant level within a desired range for a period of time so that the proton pump inhibitor can be absorbed from the gastric or other environment. Accordingly, the Essential Buffer is generally more rapid in its complexation with HCl (or other acid) than the proton pump inhibitor administered so that the Essential Buffer is capable of protecting the proton pump inhibitor.

Any weak base, strong base, or combination thereof may be a suitable Essential Buffer. Essential Buffers include, but are not limited to, electrolytes containing the cations sodium, potassium, calcium, magnesium or bismuth. In addition, amino acids, proteins or protein hydrolysates can serve as Essential Buffers owing to their ability to rapidly neutralize acid. When proton pump inhibiting agents are mixed with the Essential Buffer, the proton pump inhibiting agents may be in the free base form, such as omeprazole or lansoprazole; in the sodium salt form, such as esomeprazole sodium, omeprazole sodium, rabeprazole sodium, pantoprazole sodium, etc.; or in a magnesium salt form such as esomeprazole magnesium or omeprazole magnesium or calcium salt forms; or other salt forms. Essential Buffers provide the Essential Buffering Capacity either alone or in combination with Secondary Essential Buffers.

Tribasic sodium phosphate and sodium carbonate are examples of Secondary Essential Buffers for adjusting the pH of any Primary Essential Buffer. Secondary Essential Buffers may assist the Primary Essential Buffer in producing the desirable pH_E over the dwell time. Secondary Essential Buffers neutralize HCl (or other acids in the environment) similarly to the Primary Essential Buffers; however, they produce pH values too high to be used alone, as they would lead to gastrointestinal mucosal irritation. They are used to increase the pH and provide additional buffering capacity in combination with a Primary Essential Buffer.

Secondary Essential Buffers do not play an important role in protecting the proton pump inhibitor from early acid-induced degradation. Because they do not work as rapidly, they do not play a major role in proton pump inhibitor protection through the dwell time. Other buffers ("Non-Essential Buffers") can be added to the Primary and/or Secondary Essential Buffers to provide a latent antacid effect that extends beyond the antacid effect of Essential Buffers.

Many additional buffers can be used, alone or in combination, to achieve an effective buffering capacity for proton pump inhibiting agents or acid labile drugs. A desirable characteristic of buffers includes rapid neutralization of acid environments to greater than pKa+0.7 for the drug being considered.

Non-limiting examples of Primary and Secondary Essential Buffers are set forth in Tables 8 and 9 below.

TABLE 8

Examples of Primary Essential Buffers

Essential Buffer	Solubility‡	pH§	MW
Sodium bicarbonate	9.96 g/100 mL	8–8.4	84
Sodium sesquicarbonate	6.3 g/100 mL	9.9–10	174
Dibasic sodium phosphate	10 g/100 mL	8.6–9.3	142
Sodium tripolyphosphate	6 gm/100 mL	9.7–10	368
Tetrasodium pyrophosphate	5 g/100 mL	9.8–10.3	266
Sodium citrate	72 g/100 mL	5	294
Calcium citrate	10 mg/100 mL	6.8	498
Calcium carbonate	1.5 mg/100 mL	6.1–7.1	100
Magnesium oxide	0.62 mg/100 mL	9.5–10.5	40
Sodium gluconate	60 g/100 mL	6–8	218
Sodium lactate	40 g/100 mL	7	112
Sodium acetate	119 g/100 mL	8.9	82
Dipotassium phosphate	150 g/100 mL	9.3	174
Tetrapotassium pyrophosphate	185 g/100 mL	10.4	330
Potassium bicarbonate	36 g/100 mL	8.2	100
Calcium lactate	6 g/100 mL	7	218
Calcium glycerophosphate	6 g/100 mL	7	210
Calcium gluconate	3 g/100 mL	7.4	430
Magnesium lactate	10 g/100 mL	5.5–7.5	269
Magnesium gluconate	16 g/100 mL	7.3	414

‡solubility is altered by temperature

§pH is altered by concentration and temperature

Note:

hydrated and anhydrous forms are acceptable provided they meet the criteria of a Primary Essential Buffer.

TABLE 9

Examples of Secondary Essential Buffers These buffers are too caustic to be used alone but are suitable for addition in low quantities to the Primary Essential Buffers from Table 8.			
Essential Buffer	Solubility‡	pH§	MW
Sodium carbonate	45.5 g/100 mL	10.6–11.4	106
Potassium carbonate		11.5	138
Sodium phosphate (tribasic)	8 g/100 mL	10.7–12.1	163
Calcium hydroxide	185 mg/100 mL	12	74
Sodium hydroxide		11.4–13.2	40

‡solubility is altered by temperature

§pH is altered by concentration and temperature

Note:

hydrated and anhydrous forms are acceptable provided they meet the criteria of a Secondary Essential Buffer.

Amino acids can also be employed as Primary or Secondary Essential Buffers, the doses of which may be calculated according to the following information.

TABLE 10

One Letter Symbol	Three Letter Symbol	Amino Acid	MW	pH	Solubility (g/100 g H2O at 25° C.
A	Ala	Alanine	89	6	16.65
C	Cys	Cysteine	121	5.02	Very
D	Asp	Aspartic Acid	133	2.77	0.778
E	Glu	Glutamic Acid	147	3.22	0.864
F	Phe	Phenylalanine	165	5.48	2.965
G	Gly	Glycine	75	5.97	24.99
H	His	Histidine	155	7.47	4.19
I	Ile	Isoleucine	133	5.94	4.117
K	Lys	Lysine	146	9.59	Very
L	Leu	Leucine	131	5.98	2.426
M	Met	Methionine	149	5.74	3.381
N	Asn	Asparagine	132	5.41	3.53
P	Pro	Proline	115	6.30	162.3
Q	Gln	Glutamine	146	5.65	2.5
R	Arg	Arginine	174	11.15	15
S	Ser	Serine	105	5.68	5.023
T	Thr	Threonine	119	5.64	Very
V	Val	Valine	117	5.96	8.85
W	Trp	Tryptophan	204	5.89	1.136
Y	Tyr	Tyrosine	181	5.66	0.0453

References:

IUPAC-IUB Commission on Biochemical Nomenclature (CBN), Rules for Naming Synthetic Modifications of Natural Peptides, (1966); ARCH. BIOCHEM. BIOPHYS. 121:6–8 (1967); BIOCHEM. J. 104:17–19 (1967), corrected 135:9 (1973); BIOCHEMISTRY 6:362–364 (1967); BIOCHIM. BIOPHYS. ACTA 133:1–5 (1967); BULL. SOC. CHIM. BIOL. 49:325–330 (1967) (in French); EUR. J. BIOCHEM. 1:379–381 (1967), corrected 45:3 (1974); Hoppe-Seyler's, Z., PHYSIOL. CHEM. 348:262–265 (1967) (in German); J. BIOL. CHEM. 242 555–557 (1967); MOL. BIOL. 2:466–469 (1968) (in Russian); PURE APPL. CHEM. 31:647–653 (1972); *IUPAC Commission on Nomenclature of Organic Chemistry (CNOC), Nomenclature of Organic Chemistry,* STEREOCHEM. REC. E: (1974), PURE APPL. CHEM. 45:11–30 (1976). See also *Biochemical Nomenclature and Related Documents,* PORTAND PRESS. 2:1–18 (1992).

C. The Essential pH (pH_E)

Substituted benzimidazole proton pump inhibiting agents are labile under acidic conditions. Orally administered proton pump inhibiting agents must be protected from the strongly acidic conditions of the stomach, whether acidic from gastric acids or acids introduced through tube feeds or other sources. In general, the higher the pH of the gastric environment, the greater the stability of the proton pump inhibitor, and thus the more time it has to undergo absorption into the blood and reach and act upon the proton pumps of the gastric parietal cells.

As mentioned, the "Essential pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the proton pump inhibitor during the dwell time in the environment. It is generally expressed herein as pH range. Such pH is the pH of the environment in which the proton pump inhibitor/buffer formulation resides. For example, the environment may be a storage container or the stomach. The environment presents a set of conditions to the proton pump inhibitor/buffer, such as temperature, pH, and the presence or absence of water. The dwell time is the time that the proton pump inhibitor dwells in a specific environment, i.e., the GI tract prior to its passage into a different environment, i.e. the blood serum. The shelf-life is another example of a dwell time, in which case, the specific environment may be a container of dry, powdered formulation. As used herein, "Resultant pH" is the pH that is the result of adding a proton pump inhibitor/buffer formulation to an environment of interest. "Formulation pH" is the pH of the proton pump inhibitor/buffer formulation when it is in liquid form.

A proton pump inhibitor dose within its calculated pH_E range is designed to ensure sufficient proton pump inhibitor protection from acid degradation such that delivery to and action upon proton pumps occur. In one desirable embodiment, the pH_E is the sum of the pKa of a given proton pump inhibitor plus about 0.7. The pKa is defined as the pH at which 50% of a chemical is in the ionized form. When the pH of the environment equals the pKa of the proton pump inhibitor, then 50% ionization (degradation) of the proton pump inhibitor occurs. However, by adding the factor of 0.7, this ionization is reduced to 90%.

The Stability Range Factor ("SRF") is the range of pH elevation in which the lower limit is the sum of the pKa of a given proton pump inhibitor+0.7 log, and the upper limit is the pH at which elimination of acid degradation occurs without producing tissue irritation from extreme alkalinity. SRF is calculated based on the desirable shelf-life (or a dwell time), the environmental pH and the amount of acid expected to be encountered, along with a knowledge of the time of exposure expected after the drug is administered and before the drug reaches the blood (i.e., the dwell time).

The upper limit of the SRF is a function of the tolerability of the gastrointestinal mucosa to alkaline substances, which is determined by the Formulation pH and the concentration of alkaline material presented. For practical purposes, pH=10.9 delineates an upper limit of the SRF. It is acknowledged that the amount of buffer is an important aspect of the tissue destructive potential of an alkaline substance. Therefore, the SRF for any given proton pump inhibitor begins at the sum of the pKa of the proton pump inhibitor+0.7, and extends upwards to a pH of about 10.9.

The Essential pH used with the SRF establishes a desirable range for the stability to the actions of H+ ion (or other acidic component) on the proton pump inhibitor/buffer formulation.

Sufficient buffering capacity maintains an Essential pH as described below as "Essential Buffering Capacity."

Examples of pH_E calculations with SRF for specific proton pump inhibiting agents are as follows:

pH_E of proton pump inhibitor=pKa of proton pump inhibitor+0.7.

SRF=the range: pH_E to 10.9.

SRF for omeprazole=(pKa omeprazole+0.7) to 10.9=(3.9+0.7)=4.6 to 10.9.

SRF for lansoprazole=(pKa lansoprazole+0.7) to 10.9=(4.1+0.7)=4.8 to 10.9.

SRF for rabeprazole=(pKa rabeprazole+0.7) to 10.9=(4.9+0.7)=5.6 to 10.9.

SRF for pantoprazole=(pKa pantoprazole+0.7) to 10.9=(3+0.7)=3.7 to 10.9.

In most instances, the lower end of each of the above ranges is increased by one pH unit to minimize, by a factor of 10, any local effects within the stomach that may produce areas of lower pH that might cause proton pump inhibitor degradation. A value of +1 log value is also supported by the observation that weak bases operate most efficiently at neutralizing acid beginning at +1 log value above the pKa.

For example, one would expect to encounter about 100–150 ml of 0.11 to 0.16N HCl in the adult fasting stomach, which is equivalent to about 12–24 mEq of HCl. Therefore, an equal amount of base will neutralize this acid. If about 12–24 mEq of sodium bicarbonate is employed as the buffer, the resulting pH will be left at the pKa of the conjugate acid of sodium bicarbonate (carbonic acid), which is about 6.14 or greater. This is greater than the lower limit of the pH_E for omeprazole of 4.6. Thus, administering 12–24 mEq of sodium bicarbonate with omeprazole protects greater than 95% of the drug when encountering 12–24 mEq of HCl. Because sodium bicarbonate complexes with HCl at a rate that exceeds the rate of interaction of omeprazole, it is considered a suitable buffer.

It should be noted that depending on age and disease, the amount of acid to be encountered can be significantly more or less than the 12–24 mEq range, but is generally from about 4 mEq to about 30 mEq.

Using magnesium oxide or magnesium hydroxide in an amount of 12 to 24 mEq also provides sufficient neutralizing capacity leaving the pH at approximately 7 (lowered only slightly by the minimal hydrolysis of magnesium). However, magnesium hydroxide is not rapid in onset and care should be taken to ensure that early degradation of the proton pump inhibitor does not occur. Early degradation can be avoided by making a tablet comprising two layers: an inner layer of proton pump inhibitor and sodium bicarbonate, and an outer layer of magnesium hydroxide dried gel or magnesium oxide with suitable disintegrant such that the magnesium oxide would rapidly disintegrate in the stomach. Alternatively, the inner layer can contain the magnesium buffer and the outer layer has the proton pump inhibitor and sodium bicarbonate.

Additionally, micronization of the slower acting buffer can be used to enhance its ability to combine with acid. Calcium carbonate (and many other calcium buffers) is a similar slower acting (compared to sodium bicarbonate) but potent buffer. Therefore, if used, it would be best suited in an outer layer of a tablet formulation with the inner layer comprising a rapid acting buffer with proton pump inhibitor (or vice versa). Alternatively, mixtures of the buffers can be employed for the outer layer. If developing a liquid formulation or a powder for reconstitution, a mixture of a rapid acting buffer and slower acting buffer can be used (e.g., sodium bicarbonate and magnesium oxide, respectively).

Modifications to the formulations may entail adjusting the pH of products with basic or acidic chemicals, including but not limited to, chemicals described throughout this application. Modifications of buffer pH based on the pH_E may or may not be performed in specific instances, depending upon species, age, disease and other variations between patients.

D. pKa and Solubility of Proton Pump Inhibiting Agents

As mentioned above, the pKa of a given proton pump inhibitor indicates inherent stability with respect to acid degradation; the lower the pKa, the more stable the proton pump inhibitor. The solubility of the proton pump inhibitor will also dictate the rate at which the proton pump inhibitor complexes with, and is degraded by, acid. These two physicochemical characteristics (pKa and solubility) of the proton pump inhibitor interact with the physicochemical characteristics of the buffer(s) (pH, buffering capacity and rate of buffering action) in the presence of acid in the environment to determine the degradation of the proton pump inhibitor over time. The less soluble a proton pump inhibitor is in water, the lower the initial degradation when placed in an acidic environment. The following Table 11 elaborates on the time for 50% of drug to be degraded ($t_{1/2}$), pKa and solubility in water of several proton pump inhibiting agents.

TABLE 11

PH	Pantoprazole	Omeprazole	Lansoprazole	Rabeprazole
	sodium			sodium
1.2	4.6 min	2.8 min	2.0 min	1.3 min
5	2.8 hr	1.0 hr	1.1 hr	
5.1	4.7 hr	1.4 hr	1.5 hr	7.2 minutes
6	21 hr	7.3 hr	6.4 hr	
7	73 hr	39 hr	35 hr	
PKa	3	3.9	4.1	4.9
Solubility	very soluble	slightly soluble	very slightly soluble	Very soluble

Kromer W, et al. Differences in pH-Dependent Activation Rates of Substituted Benzimidazoles and Biological in vitro Correlates, PHARMACOLOGY 1998; 56:57–70.

Although pantoprazole sodium, with a pKa of 3, is inherently more stable in an acidic environment than other proton pump inhibiting agents, it is also very soluble in water and thus could undergo 50% degradation in an acidic stomach with a pH of 1.2 in less than 5 minutes. Therefore, it is important for the buffer(s) used with pantoprazole sodium to interact with H+ ion (or other acidic substances) more rapidly than the pantoprazole sodium interacts with such acids and maintain the rapid complexation through the dwell time; otherwise, additional dosing of buffer may be required. The overall pH of the gastric contents should be kept at least at the pKa+0.7 (i.e., 3.7) from the time the proton pump inhibitor in solution comes into contact with the gastric acid continuing throughout the dwell time. Essential Buffers for liquid formulations of pantoprazole sodium include those buffers whose conjugate acids possess a pKa>3.7 and which are very soluble (e.g., potassium bicarbonate and sodium bicarbonate) Oral solid formulations likewise would require buffers whose conjugate acid possesses a pKa>3.7 and rapid complexation potential. Most magnesium, calcium and aluminum salts are not suitable unless the pantoprazole sodium is placed (with or without additional buffer) in an inner portion of a tablet or capsule with such antacids, and surrounded by a rapid acting buffer with a rapid disintegrant. Another formulation method for pantoprazole is to decrease its solubility such as by selecting a less soluble salt form or the non-salt form, pantoprazole.

Rabeprazole sodium is also very soluble in water and could undergo 50% degradation in an acidic stomach with a pH of 1.2 in less than 1.5 minutes. It is not very stable to acid degradation due to its higher pKa of 4.9. A suitable buffer(s) for rabeprazole sodium interacts with H+ ion (or other acidic substances) more rapidly than the rabeprazole sodium interacts with such acids to prevent early degradation, and should possess high neutralizing capacity to enable rabeprazole to

survive through the dwell time. Sodium or potassium bicarbonate would be good choices in this instance.

Another option for rabeprazole sodium (as well as any sodium salt of a proton pump inhibitor, which would tend to be more soluble than the base form) is to reduce the solubility of rabeprazole sodium when in aqueous form such as using a less soluble salt form or using the non-salt form. This decreases early degradation because the rabeprazole must first undergo dissolution in water before it is degraded by acid. In this embodiment, the suitable buffer(s) for rabeprazole sodium should possess high neutralizing capacity to enable rabeprazole to survive through the dwell time.

For proton pump inhibiting agents that possess high pKa's, such as rabeprazole sodium, a two-part liquid formulation can be utilized. The liquid part has the proton pump inhibitor and a high pH, but a low mEq buffering capacity. The liquid part is added to a second part that possesses a lower pH but a higher mEq buffering capacity. When these two parts are added together just prior to administration, a formulation with a lower pH and a higher buffering capacity is produced which will neutralize stomach acid but not be too caustic to tissues. Examples of such formulations are provided below.

For highly soluble proton pump inhibiting agents, the formulation may be produced in a solid dosage form such as a tablet, capsule or powder with a buffer(s), which disintegrate and reach solution at a rate that exceeds the proton pump inhibitor and thereby provides the Essential pH for protection of the proton pump inhibitor prior to its dissolution and interaction with the acid in the environment. Further, the tablet or capsule may be formulated to possess an outer portion of buffer and an inner portion comprising proton pump inhibitor, or a blend of proton pump inhibitor and buffer. Additional methods include formulating the buffer in a smaller particle size (e.g., micronized) and the proton pump inhibitor in a larger particle size. This results in the disintegration of the buffer component prior to disintegration of the proton pump inhibitor component. All of these methods of formulation aim to create an environment of stability for the proton pump inhibitor during the dwell time.

The dosage form may affect the suitability of a buffer for use in a formulation. For example, magnesium oxide is a buffer with high buffering capacity but slow onset when formulated as a tablet. However, when formulated as a powder, or a tablet of low compression, or with tablet disintegrants such as pregelatinized starch, it disintegrates more rapidly.

Omeprazole base is only slightly soluble in water and, as such, less of the drug is subject to early and continued degradation. The soluble portion of omeprazole is vulnerable to early degradation in the gastric environment. Dissolution of the remaining insoluble portion is expected to occur within minutes of encountering the water of the gastric secretions. This dissolution time provides some protection against early degradation provided that relatively low volumes of water are used during delivery or in the product formulation. After several minutes in the gastric environment, upon complete dissolution, omeprazole could undergo 50% degradation in less than 3 minutes. Omeprazole is moderately stable owing to its pKa of 3.9. A suitable buffer(s) for omeprazole is rapid acting and possesses at least moderate neutralizing capacity to enable omeprazole to survive through the dwell time.

As used herein, "rapid acting" in the context of a buffer means a buffer that raises the pH of the environment to greater than or equal to the pH_E of a particular proton pump inhibitor in a time sufficient to prevent significant degradation of the proton pump inhibitor. In one embodiment, the rapid acting buffer raises the pH to at least the pKa of the proton pump inhibitor plus 0.7 log value within 10 minutes.

Preferred buffer(s) produce an environment where the Resultant pH of the environment is equal to or greater than the Essential pH such that: (1) the onset of pH change to equal to or greater than the pH_E+0.7 begins before the acid-induced degradation of the proton pump inhibitor occurs, and (2) the Resultant pH at or greater than the pH_E+0.7 lasts throughout the dwell time, which is typically a minimum of 30 minutes in the case of gastric emptying for an adult. It is desirable that the buffer be rapid acting to minimize early acid-induced degradation. The most rapid acting buffers are water soluble (or soluble in the environment). High solubility, however, is not an absolute necessity as magnesium oxide and calcium carbonate, both only slightly soluble, are capable of significant complexation with gastric acid albeit at a slower rate. If a dry formulation is used, such as a tablet, the particle size of the buffer(s) can be reduced to enhance the dissolution rate while the particle size of the proton pump inhibitor can be increased. Disintegrants can be added to enhance the availability of poorly soluble buffers.

Lansoprazole base is very slightly soluble in water and, as such, less of the drug is subject to early degradation. The soluble portion is vulnerable to early degradation. Dissolution of the remaining insoluble portion is expected to occur within several minutes of encountering the water of the gastric secretions. This dissolution time provides some protection against early degradation provided that relatively low volumes of water are used for delivery or in the product formulation. After several minutes, upon complete dissolution, lansoprazole could undergo 50% degradation in 2 minutes. Lansoprazole is moderately stable owing to its pKa of 4.1. A suitable buffer(s) for lansoprazole should be rapid acting, and should possess moderate to high neutralizing capacity to enable lansoprazole to survive through the dwell time. The pH of the gastric contents (or other environment) should be kept at greater than about 4.8 from the time the proton pump inhibitor in solution comes into contact with the gastric acid continuing throughout the dwell time.

E. Calculating the Acid Neutralizing Capacity of Buffers

The acid neutralizing capacity ("ANC") of soluble buffers may be used to assist in selecting a preferred amount of buffer(s) needed to provide the EBC. The ANC uses both the formula weight (FWt.) and the valence to determine buffering capacity.

An example of an ANC calculation for sodium bicarbonate is as follows:

Sodium Bicarbonate, $Na^+HCO_3^-$, FWt.=84, valence=1. The conversion equation from equivalent weight to grams is:

(Equivalent Weight ("EW"))(1/1000 mmol)(1 mmol/1 mEq)=grams of $NaCHO_3$

EW=(FWt.)/(valence)=84/1=84 g/mol.

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 mEq)=0.34 g $NaHCO_3$ needed for 4 mEq of buffering capacity.

Accordingly, for 10 mEq, one needs 0.840 g $NaHCO_3$, and for 30 mEq, 2.52 gm is required. The range of 4–30 m Eq is used because that is the range of mEq of acid to be encountered in most patients.

The ANCs of other buffers are similarly calculated. ANC determinations are from Drake and Hollander, *Neutralizing Capacity And Cost Effectiveness Of Antacids,* ANN

INTERN. MED. 109:215–17 (1981). Generally, the formulations of the present invention need about 4 to about 30 mEq of buffering capacity although higher amounts could be used in some patients.

Sodium bicarbonate in solution possesses a pH>pH_E of omeprazole and rapidly neutralizes acidic environments. As stated above, rapid complexation with HCl is a desirable characteristic of an Essential Buffer. Ideally, but not necessarily required as indicated in formulations that contain a tablet in a tablet, the Essential Buffer complexes with the acid at a faster rate than the proton pump inhibitor it is intended to protect.

In selecting Essential Buffers, a knowledge of buffering capacity is also useful since they possess differing pHs at various concentrations. The magnitude of the resistance of a buffer to pH changes is referred to as buffer capacity (Beta). It has been defined by Koppel, Spiro and Van Slyke as the ratio of the increment of strong acid (or base) to the change in pH brought about by addition of acid. The following formula is used to measure buffer capacity: Buffer capacity= the increment (in gram equivalents per liter) of strong acid added to the buffer solution to produce a pH change (change as measured in absolute terms), or buffer capacity=change in acid/change in pH. Improvements in the formula have been made to improve the precision, and these form the basis for mathematical comparison of buffers for consideration. See Koppel, BioChem, Z. (65) 409–439 (1914), Van Slyke, J. BIOL. CHEM. 52:525 (1922).

When the proton pump inhibitor/buffer formulation is placed in the environment, the proton pump inhibitor is subject to degradation by the acid in that environment. As depicted in FIG. 9, proton pump inhibitor solubility, the pKa of the proton pump inhibitor, and the amount and concentration of acid (H+ ion) encountered in the environment are variables that can be used to determine the appropriate candidate as an Essential Buffer. Early degradation occurs when the soluble portion of the proton pump inhibitor (that portion available for immediate interaction with H+ ion) undergoes hydrolysis by H+ ion. proton pump inhibiting agents differ in their solubility and, therefore, those that are more soluble have a potential for a higher portion of proton pump inhibitor degraded by early interaction with H+ ion. The pKa of the proton pump inhibitor and the pH of the environment of the stomach (or other site of interest) after addition of the proton pump inhibitor/buffer formulation (Resultant pH) can be used to determine the desirable Essential Buffer. By measuring the Resultant pH over time, the pH data versus time can be plotted as seen in FIG. 9. The graph of pH over time can then be used to evaluate various buffers.

Such a graph can be developed for a potential buffer or buffer combination using the Rossett-Rice test (Rosset N E, Marion L: *An In Vitro Evaluation Of The Efficacy Of The More Frequently Used Antacids With Particular Attention To Tablets.* ANTACIDS 26:490–95 (1954), modified with continual addition of simulated gastric fluid. See USP XXIII, *The United States Pharmacopeia*, 23rd Revision, United States Pharmacopeia Convention, Inc. Briefly, the test employs 150 mL of simulated gastric fluid consisting of 2 Gm of sodium chloride and 3.2 Gm of pepsin, which are dissolved in 7 mL of 1N HCl, q.s. to 1000 mL with distilled water. The pH of the simulated gastric fluid is 1.2. A container of 150 mL of this fluid is stirred at 300 rpm±30 rpm with a magnetic stirrer and kept at 37.1° C. A pH electrode is kept in the upper region of the solution. The test buffer or the subject formulation is added to the container to start the evaluation. At 10 minutes, a continuous drip of simulated gastric fluid is added to the test container at a rate of 1.6 ml/min to simulate gastric secretion. Approximately 1.6 mL/min is removed from the test container to keep the volume in the test container constant. The evaluation continues for at least 90 minutes.

This methodology allows for a dynamic evaluation of buffering capacity in a model designed to mimic a fasting human stomach. It has been described in part for use in evaluating antacids by Beneyto J E, et. al., *Evaluation of a New Antacid, Almagate, ARZNEIM-FORSCH/DRUG RES* 1984; 34 (10 A):1350–4; Kerkhof NJ, et al, *pH-Stat Tiration of Aluminum Hydroxide Gel,* J. PHARM. SCI. 1977; 66:1528–32.

Using this method, a pH tracing can be developed for evaluating buffers as well as finished products. In addition, a sample of the test solution can be taken during the experiment to evaluate the extent of proton pump inhibitor degradation at various times. Those buffers with a suitable profile as exemplified in FIG. 9 able to maintain pH greater than or equal to pH_E for 30 minutes or greater, can be considered suitable Essential Buffers. In one embodiment, as depicted in FIG. 9, the pH was recorded over 10 second intervals.

A number of buffers may be applicable for use as Essential Buffers. Therefore, once an Essential Buffer is chosen, the amount necessary to provide the EBC is calculated. As used herein, the EBC is the buffering capacity, or amount of alkaline buffer, included in the dose and calculated to maintain the Essential pH range and thereby protect any substituted benzimidazole. proton pump inhibitor in the gastric (or other) environment. In patients requiring continuing proton pump inhibitor administration (e.g. daily), more buffering capacity may be necessary with the first dose or first few doses than with subsequent doses because the proton pump inhibitor may encounter more acid with the initial doses. Subsequent doses will require less buffering capacity because the initial proton pump inhibitor doses will have reduced gastric acid production. The EBC could therefore be reduced in subsequent doses. The product's buffering capacity may be formulated as desired, for instance with respect to patient age, gender or species.

Experimental data from adult human subjects showed an effective EBC range of a first dose of omeprazole to be about 4 to about 20 mEq ("EBC-O range") of sodium bicarbonate, with a range of about 12 to about 25 mEq suitable in most instances. Subsequent doses of omeprazole require less EBC, with a range of about 4 to 15 mEq sodium bicarbonate. In one embodiment, this latter EBC range proved optimal for an omeprazole suspension administered to patients with varying degrees of gastrointestinal transit and acid output, based on a knowledge of basal and maximal acid outputs of 2 and 25 mEq/hour, respectively. These studies have been reported in Phillips J. O. et al., CRIT. CARE MED. 1996; Lasky et al., J. TRAUMA 1998.

Based on the EBC-O range, the above ANC calculation can be employed. Additionally, it is expected to encounter about 100–150 mL of 0.1 N HCl (equating to about 12–24 mEq of acid) in a fasting stomach. Variations in the acid encountered in the environment will affect the Essential Buffering Capacity required. The above EBC ranges relate to adult patients. Children, however, produce less acid per unit time in comparison to adults. Therefore, depending on the patient population, the amount of Essential Buffering Capacity required may be altered.

Numerous references are available to assist the skilled artisan in identifying a suitable buffer companion with a proton pump inhibitor to determine the desirable character-

istics stated herein. See, e.g., Holbert, et. al., *A Study of Antacid Buffers: I. The Time Factor in Neutralization of Gastric Acidity*, J. AMER. PHARM. ASSN. 36:149–51 (1947); Lin, et. al., *Evaluation of Buffering Capacity and Acid Neutralizing pH Time Profile of Antacids*, J. FORMOSA MED. ASSN. 97 (10) 704–710 (1998); *Physical Pharmacy*, pp 169–189; *Remington: The Science and Practice of Pharmacy* (2000).

F. The Desirable Volume

The Desirable Volume ("DV") of a proton pump inhibitor dose may affect proton pump inhibitor delivery to and action upon parietal cell proton pumps. The DV of a dose is partly based on the EBC. For liquid formulations, a desirable volume should deliver sufficient buffer to act as an antacid to neutralize a substantial amount of gastric or other acids. For solid formulations such as tablets, a nominal amount of water or other fluid will be consumed to aid in swallowing the tablet. Liquid preparations of the present invention use volumes as small as about 2 ml or in excess of about 60 ml. Volumes smaller than 2 ml and larger than 60 ml are contemplated, and may be used as desired to suit individual patients, such as those of advanced or very young age or of different species. Very large volumes may lead to higher amounts of less soluble proton pump inhibiting agents (e.g., omeprazole, lansoprazole base forms) going into solution, which could result in vulnerability to early degradation.

For instance, volumes smaller than about 2 ml may be used in newborns or premature infants, or in small animals, because of their smaller stomach size. Also, a large DV may be required for doses formulated with dilute buffer concentrations, to achieve the EBC. The relationship between the EBC and DV is in part shown below:

If EBC(mg buffer)=Buffer conc.(mg/ml)×DV(ml),

then DV(ml)=EBC(mg)/Buffer conc.(mg/ml).

Alternatively, mEq can be substituted for mg in the formula.

G. Secondary Components of the Formulations

Secondary components are not required but may be used to enhance the pharmacological action or as pharmaceutical aids. Secondary components may include, but are not limited to, parietal cell activators and other ingredients. Parietal cell activators, as discussed above, are compounds that produce an increase in proton pump activity such that proton pumps are relocated from storage sites of the parietal cell, i.e. tubulovesicles, to the site of H+, K+ exchange at the secretory canaliculus. A parietal cell activator may also serve other functions. For example, sodium bicarbonate is an Essential Buffer as well as a parietal cell activator, chocolate is a parietal cell activator and a flavoring agent, and aspartame, which contains phenylalanine, is a sweetener as well as a parietal cell activator.

Parietal cell activators can be divided into four groups: 1) rapid acting buffers that are weak bases, strong bases or combinations thereof that also produce a rapid onset of effect (the pH drops rather suddenly after the buffer is exhausted; these buffers typically cause the pH of the stomach to rise to above 5); 2) amino acids, protein hydrolysates and proteins; 3) calcium containing compounds such as calcium chloride or calcium carbonate; and 4) compositions such as coffee, cocoa, caffeine and peppermint.

The other ingredients comprise components of a formulation that are secondary to the primary components. Other ingredients include, but are not limited to, thickening agents, flavoring agents, sweeteners, antifoaming agents (such as simethicone), preservatives, antibacterial or antimicrobials agents (such as cefazolin, amoxicillin, sulfamethoxazole, sulfisoxazole, erythromycin and other macrolides such as clarithromycin or azithromycin), and Secondary Essential Buffers.

Desirable flavoring agents may be added to the dosage forms, and may or may not need to be buffered to the pH_E. Flavoring agents with pH values inherently suitable to the range of pH_E values of proton pump inhibiting agents include, but are not limited to, apple, caramel, meat, chocolate, root beer, maple, cherry, coffee, mint, licorice, nut, butter, butterscotch, and peanut butter flavorings, used alone or in any combination. Similarly, all substances included in the formulation of any proton pump inhibitor product, including but not limited to, activators, antifoaming agents, potentiators, antioxidants, antimicrobial agents, chelators, sweeteners, thickeners, preservatives, or other additives or substances may be buffered to the pH_E.

H. Examples Utilizing the Calculations

The pH_E, the EBC, and the DV of a proton pump inhibitor dose may affect proton pump inhibitor delivery to, and action upon, parietal cell proton pumps. The following calculations tailor an Essential Buffer dose for any substituted benzimidazole proton pump inhibitor to promote proton pump inhibitor efficacy in an oral administration.

Example 1: To deliver a 20 mg dose of omeprazole (pKa=3.9) in sodium bicarbonate:

Step 1: The pH_E of omeprazole=pKa of omeprazole+0.7=4.6. The SRF of omeprazole=pH_E to 10.9=4.6 to 10.9. At a Formulation pH of 4.6 to 10.9, the conjugate base of sodium bicarbonate (carbonic acid) has a pKa of 6.14. Therefore, an amount of sodium bicarbonate equivalent to the amount of acid to be encountered would produce a pH of 6.14, which is within the SRF of 4.6 to 10.9. Sodium bicarbonate would make a suitable choice as a buffer.

Step 2: The EBC=4 to 30 mEq buffering capacity equivalent.

Step 3: To determine the amount of sodium bicarbonate to administer with the omeprazole, the ANC for sodium bicarbonate is calculated. The ANC for sodium bicarbonate (MW=84 for 4–30 mEq)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC)

EW=MW/(valence)=84/1=84 g/mol

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.34 g to 2.52 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=Essential Buffer (EB) (mg)/Buffer conc. (mg/ml)

Buffer conc.=EB/DV=340 mg to 2520 mg/20 ml=17 mg/ml to 126 mg/ml.

Therefore, for 20 mg of omeprazole to be adequately buffered in 20 ml of solution, the concentration of sodium bicarbonate should be 17 to 126 mg/ml.

Example 2: To deliver a 20 mg dose of omeprazole (pKa=3.9) in dibasic sodium phosphate:

Step 1: The pH_E of omeprazole=pKa of omeprazole+0.7. The SRF of omeprazole=(3.9+0.7) to 10.9=4.6 to 10.9.

Step 2: The EBC=4 to 30 mEq buffering capacity equivalent.

Step 3: To determine the amount of dibasic sodium phosphate to administer with the omeprazole, the ANC for dibasic sodium phosphate is calculated. The ANC for dibasic sodium phosphate (MW=142)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC).

EW=MW/(valence)=142/2=71 g/mol.

(71 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.28 g to 2.13 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml)

Buffer conc.=EB/DV=280 mg to 2130 mg/20 ml=14 mg/ml to 107 mg/ml.

Therefore, for 20 mg of omeprazole to be adequately buffered in 20 ml of solution, the concentration of dibasic sodium phosphate should be 14 to 107 mg/ml. The pka of disodium phosphate is 7.21. Therefore, an amount of disodium phosphate equivalent to the amount of acid to be encountered would produce a pH of approximately 7.2. Thus, disodium phosphate would make a suitable choice as a buffer.

Example 3: To deliver a 30 mg dose of lansoprazole (pKa=4.1) in sodium bicarbonate:

Step 1: The pH_E of lansoprazole=pKa of lansoprazole+0.7. The SRF of lansoprazole=(4.1+0.7) to 10.9=4.8 to 10.9.

Step 2: The EBC=4–30 mEq buffering capacity equivalent.

Step 3: To determine the amount of sodium bicarbonate to administer with the lansoprazole, the ANC for sodium bicarbonate is calculated. The ANC for sodium bicarbonate (MW=84)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC)

EW=MW/valence=84/1 g/mol

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.34 g to 2.52 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml)

Buffer conc.=EB/DV=340 mg to 2520 mg/20 ml=17 mg/ml to 126 mg/ml.

Therefore, for 30 mg of lansoprazole to be adequately buffered in 20 ml of solution, the concentration of sodium bicarbonate should be about 17 to about 126 mg/ml.

Example 4: To deliver a 40 mg dose of pantoprazole (pKa=3) in sodium bicarbonate:

Step 1: The pH_E of pantoprazole=pKa of pantoprazole+0.7. The SRF of pantoprazole=(3+0.7) to 10.9=3.7 to 10.9.

Step 2: The EBC=4–30 mEq buffering capacity equivalent.

Step 3: To determine the amount of sodium bicarbonate to administer with the pantoprazole, the ANC for sodium bicarbonate is calculated. The ANC for sodium bicarbonate (MW=84)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC)

EW=MW/(valence)=h 84/1 g/mol

(84 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 30 mEq)=0.34 g to 2.52 g

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml)

Buffer conc.=EB/DV=340 mg to 2520 mg/20 ml=17 mg/ml to 126 mg/ml.

Therefore, for 40 mg of pantoprazole to be adequately buffered in 20 ml, the concentration of sodium bicarbonate should be about 17 to 126 mg/ml.

Example 5: To deliver a 20 mg dose of rabeprazole (pKa=5) in sodium phosphate dibasic:

Step 1: The pH_E of rabeprazole=pKa of rabeprazole+0.7. The SRF of rabeprazole=4.9+0.7) to 10.9=5.6 to 10.9.

Step 2: The EBC=4–30 mEq buffering capacity equivalent.

Step 3: Therefore, to determine the amount of sodium phosphate dibasic to administer with the rabeprazole, the ANC for potassium sodium dibasic is calculated. The ANC for sodium phosphate dibasic (duohydrate) (MW=174)=(EW)(1/1000 mmol)(1 mmol/1 mEq)(EBC)

EW=MW/valence=178/1 g/mol

(178 g/mol)(1 mol/1000 mmol)(1 mmol/1 mEq)(4 to 20 mEq)=0.712 g to 5.34 g sodium phosphate dibasic.

Step 4: For liquid formulations, if the DV=20 ml, then DV=EB (mg)/Buffer conc. (mg/ml).

Buffer conc.=EB/DV 0.712 g to 2 g/20 ml=35.6 mg/ml to 100 mg/ml. In this case, the solubility of disodium phosphate would limit the amount that could be dissolved in 20 mL. Obviously, this would exceed the solubility of disodium phosphate (sodium phosphate dibasic). Therefore, for 20 mg of rabeprazole to be adequately buffered in 20 ml of solution, the concentration of sodium phosphate dibasic should be about 35.6 mg/ml to 100 mg/ml at a pH range of about 6.9 to 10.9. The pka of disodium phosphate is 7.21. Thus, an amount of disodium phosphate equivalent to the amount of acid to be encountered would produce a pH of approximately 7.2. Accordingly, disodium phosphate would make a suitable choice as a buffer.

It should be noted that the suitability of buffers relates to their use immediately after mixing. In order to enhance the shelf-life, higher pH values would be anticipated within the range of acceptable pH_E for a given proton pump inhibitor. As an example, rabeprazole suspensions containing various buffers were evaluated for color change because degradation of proton pump inhibiting agents results in a color change to brown or black. All buffer suspensions started out white in color. After 2 weeks the following observations were made:

20 mg Rabeprazole in Various Buffers Stored Under Refrigerated Conditions As Suspensions

Buffer	Original Color	Color 14 days	pH at 14 days
Sodium bicarbonate 800 mg/10 mL	white	brown	8.3
Disodium phosphate 800 mg/10 mL	white	white	10.3
Disodium phosphate 700 mg; Trisodium phosphate 100 mg/10 mL	white	white	10.5

Similar calculations may be performed for any substituted benzimidazole proton pump inhibitor and appropriate buffer(s) including, but not limited to, those exemplified above. One skilled in the art will appreciate that the order of the above steps is not critical to the invention. The above calculations may be used for formulations comprising one or more proton pump inhibitor and one or more buffers.

I. Veterinary Formulations

Horses produce stomach acid continuously throughout the day. It is the basal acid secretion from the stomach in the absence of feeding that is responsible for the erosion of the squamous mucosa in the stomach and ulcers. Horses on pasture normally secrete a continuous supply of saliva, which buffers the stomach acid. When horses are being ridden regularly, trained for shows or prepared for sales, they are usually kept in stalls much of the day. Under these conditions, the natural salivary buffering mechanism is disrupted and acid indigestion often results.

Almost 40 to about 100 mEq of buffer capacity should provide approximately 2.5 hours of neutralization for a horse. The usual dose of omeprazole ranges from 0.7 to 1.5 mg/kg/day (doses up to 4 mg/kg/day may be required) and a typical weight for a horse is 500 kg. Similar dosages are expected for rabeprazole and lansoprazole.

Dogs can also suffer from ulcers and their dosage is approximately 1 mg/kg/day. The following formulations are designed for use in horses but smaller amounts can be used in dogs with an EBC of 10 to 20 mEq.

Formulation 5: Veterinary Formulation of Omeprazole
This formulation is particularly well suited for animals rather than humans because the dose of proton pump inhibitor is high. EBC = 75 mEq Essential pH (omeprazole pKa = 3.9 + 0.7 ≧ 4.6)

Proton pump inhibitor:	
Omeprazole powder	500 mg (a range of 350 to 700 mg)
Primary Essential Buffer(s):	
Sodium bicarbonate	5 g (59.5 mEq)
Dibasic sodium phosphate (anhydrous)	2 g (14 mEq)
Optional Secondary Essential Buffer(s):	
Tribasic sodium phosphate	200 mg. (1.2 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering effect.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as guar gum 350 mg, artificial maple flavor powder 100 mg, thaumatin powder 10 mg (to mask the bitterness of omeprazole), and sucrose 25 Gm. Q.s. to 100 mL with distilled water to achieve a final omeprazole concentration of 5 mg/mL. Different volumes of water may be added to achieve omeprazole concentrations ranging from about 0.8 to about 20 mg/mL.

Alternatively, this formulation may be divided into two parts. The dry part may be reconstituted with the liquid part at the time of use.

Formulation 6: Veterinary Formulation of Lansoprazole
Essential pH (lansoprazole pKa=4.1 + 0.7 ≧ 4.8)
EBC = 71.4 mEq

Proton pump inhibitor:	
Lansoprazole powder	750 mg
Primary Essential Buffer(s):	
Sodium bicarbonate	6 g (71.4 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering effect.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as xanthan gum 300 mg, artificial peanut butter flavor powder 100 mg, and sucrose 35 Gm. Q.s. to 100 mL with distilled water to achieve a final lansoprazole concentration of 7.5 mg/mL. The suspension should be refrigerated after reconstitution. Different volumes of water may be added to achieve lansoprazole concentrations ranging from 0.8 to 20 mg/mL.

Alternatively, this formulation may divided into two parts. The dry part may be reconstituted with the liquid part at the time of use.

Formulation 7: Veterinary Formulation of Lansoprazole
Essential pH (lansoprazole pKa = 4.1 + 0.7 ≧ 4.8)
EBC = 63.3 mEq

Proton pump inhibitor:	
Lansoprazole powder	750 mg

-continued

Formulation 7: Veterinary Formulation of Lansoprazole
Essential pH (lansoprazole pKa = 4.1 + 0.7 ≧ 4.8)
EBC = 63.3 mEq

Primary Essential Buffer(s)	
Sodium bicarbonate	5 g (59.5 mEq)
Secondary Essential Buffer(s):	
Sodium carbonate	400 mg* (3.8 mEq)

(* Any Secondary Essential Buffer(s) may be added to adjust pH for desired stability and additive antacid or buffering effect.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl methyl cellulose 300 mg, artificial maple flavor 100 mg, and sucrose 35 Gm. Q.s. to 100 mL with distilled water to achieve a final lansoprazole concentration of 7.5 mg/mL. Different volumes of water may be added to achieve lansoprazole concentrations ranging from 0.3 to 20 mg/mL.

Alternatively, this formulation may divided into two parts. The dry part may be reconstituted with the liquid part at the time of use.

Formulation 8: Veterinary Formulation of Esomeprazole Magnesium
Essential pH (esomeprazole pKa = 3.9 + 0.7 ≧ 4.6)
EBC = 53.2 mEq

Proton pump inhibitor:	
Esomeprazole magnesium powder	500 mg
Primary Essential Buffer(s):	
Sodium bicarbonate	5 g (47.6 mEq)
Dibasic sodium phosphate	800 mg (5.6 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl cellulose 300 mg, artificial butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water to achieve a final esomeprazole concentration of 7.5 mg/mL. Different volumes of water may be added to achieve esomeprazole concentrations ranging from 0.8 to 20 mg/mL.

Formulation 9: Veterinary Formulation of Pantoprazole Sodium or Pantoprazole Base Powder
Essential pH (pantoprazole sodium pKa = 3 + 0.7 ≧ 3.7)
EBC = 53.8 mEq

Pantoprazole sodium or pantoprazole powder	1000 mg
Primary Essential Buffer(s):	
Sodium bicarbonate	4 g (47.6 mEq)
Secondary Essential Buffer(s):	
Trisodium phosphate	1000 mg* (6.2 mEq)

(*Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl cellulose 300

mg, artificial butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water to achieve a final pantoprazole concentration of 10 mg/mL. Different volumes of water may be added to achieve esomeprazole concentrations ranging from 0.2 to 20 mg/mL.

Formulation 10: Veterinary Formulation: Buffer Base Without Proton Pump Inhibitor
EBC = 71.4 mEq

Primary Essential Buffer:	
Sodium bicarbonate	6 g 71.4 mEq
Optional Secondary Essential Buffer:	
Tribasic sodium phosphate	1000 mg*

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Powders of the above compounds are combined as is known in the art to create a homogenous mixture with the addition of a thickener such as hydroxypropyl cellulose 300 mg, artificial butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water. A proton pump inhibitor or other acid-labile drug may be added by the compounding pharmacist selected from available proton pump inhibiting agents or acid-labile drugs from powder or enteric-coated oral solid dosage forms. Different volumes of water may be added to achieve proton pump inhibitor concentrations ranging from 0.8 to 20 mg/mL. If other acid labile drugs are employed, the range of concentrations would be as required to deliver the normal dosage in an acceptable volume of 1 mL to 30 mL. The amount of buffer required to protect the drug in question will also determine the minimal feasible volume. This formulation may be in the form of a one-part product (liquid or dry) or a two-part product (liquid and dry), for examples. In the two-part example, the drug to be added to the formulation may be added to the dry formulation and the liquid part may be added at the time of use, or the drug may be added to the liquid portion which would be buffered to a pH above that required for disintegration of enteric-coated drug formulations (typically pH of 6.8 or greater).

For all of the veterinary and human oral dosage forms disclosed herein, sweeteners, parietal cell activators, thickeners, preservatives, and flavoring agents may also be added. Sweeteners include but are not limited to corn syrup, simple syrup, sugar, thaumatin, and aspartame. Thickeners include but are not limited to methylcellulose, xanthan gum, carrageenan, and guar gum. Preservatives may be added to retard spoilage and include but are not limited to sodium benzoate, methylparaben and propylparaben. Flavoring agents in these formulations include but are not limited to apple, caramel, maple, peanut butter, meat, etc.

J. Other Formulations

For all formulations herein, the total amount of Essential Buffer may range from about 4 mEq to about 30 mEq per dose.

Formulation 11: Oral Buffer Complex Without Proton Pump Inhibitor (for general use to protect acid labile drugs) Multidose Composition

Primary Essential Buffer:	
Dibasic sodium phosphate or sodium-bicarbonate	10 g (range 2 g to 10 g)
Optional Secondary Essential Buffer:	200 mg
Tribasic sodium phosphate or sodium carbonate	
Other ingredients:	
Sucrose	26 g
Maltodextrin	2 g
Cocoa processed with alkali	1800 mg
Corn syrup solids	6000 mg
Sodium caseinate	100 mg
Soy lecithin	80 mg

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet. Preservatives may be added to retard spoilage and include but are not limited to sodium benzoate, methylparaben, and propylparaben. Thickeners such as xanthan gum, guar gum, or hydroxymethyl propyl cellulose can be flavoring agents in these formulations include chocolate, caramel, maple, butter pecan and other flavorings as have been outlined previously. Different volumes of water may be added to achieve proton pump inhibitor concentrations ranging from 0.8 to 20 mg/mL.

Weigh out approximately 60 g of the formulation. Add proton pump inhibitor (or other acid-labile drug) typically in the amount equivalent to 10 doses (range 1 dose to 30 doses).

Q.s. to 100 mL with distilled water.

Formulation 12: Oral Buffer Complex Without Proton Pump Inhibitor For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Primary Essential Buffer:	
Sodium bicarbonate	5 g (range 2 g to 10 g) (59.5 mEq)
Optional: Secondary Essential Buffer	
None*	
Other ingredients	
Sucrose	26 g
Maltodextrin	2 g
Cocoa processed with alkali	1800 mg
Corn syrup solids	6000 mg
Soy lecithin	80 mg

Note that cocoa is a parietal cell activator.
(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.)

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add proton pump inhibitor (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses).

Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve proton pump inhibitor concentrations ranging from 0.8 to 20 mg/mL.

Formulation 13: Buffer Complex Without Proton Pump Inhibitor For General Use to Protect Acid Labile Drugs; Protein Free, Lactose Free Multidose Example	
Proton pump inhibitor:	
None (to be added later, e.g. by compounding pharmacist)	
Primary Essential Buffer(s):	
Sodium bicarbonate	8 g (range 2 g to 10 g)
Other ingredients:	
Sucrose	26 g
Maltodextrin	2 g
Corn syrup solids	6000 mg
Partially hydrogenated soybean oil	400 mg
Dipotassium phosphate	300 mg
Caramel flavor	270 mg
Soy lecithin	80 mg
Sodium silico aluminate	20 mg
Titanium dioxide	10 mg

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet.

Optional Secondary Essential Buffer:

Tribasic sodium phosphate 1000 mg

Weigh out approximately 60 g of the formulation. Add proton pump inhibitor (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve proton pump inhibitor concentrations ranging from 0.3 to 20 mg/mL.

Formulation 14: Buffer Complex Without Proton Pump Inhibitor For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example	
Proton pump inhibitor:	
None (to be added later, e.g. by compounding pharmacist)	
Primary Essential Buffer(s):	
Dibasic sodium phosphate	8 g (range 2 g to 10 g)
Other ingredients:	
Sucrose	26 g
Maltodextrin	2 g
Butterscotch flavor	270 mg
Corn syrup solids	6000 mg

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet.

Weigh out approximately 60 g of the formulation. Add proton pump inhibitor (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve proton pump inhibitor concentrations ranging from 0.8 to 20 mg/mL.

Formulation 15: Buffer Complex Without Proton Pump Inhibitor For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example	
Proton pump inhibitor:	
None (to be added later, e.g. by compounding pharmacist)	
Primary Essential Buffer(s):	
Sodium bicarbonate	8 g (range 1 g to 10 g)
Secondary Essential Buffer(s):	
Trisodium phosphate	1.5 g (range 0 g to 5 g)
Other ingredients:	
Sucrose	26 g
Maltodextrin	2 g
Butterscotch flavor	270 mg
Corn syrup solids	6000 mg

Thoroughly blend the powder, then store in a container protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add proton pump inhibitor (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve proton pump inhibitor concentrations ranging from 0.8 to 20 mg/mL.

Formulation 16: One Phase Lansoprazole 30 mg Tablet
Lansoprazole has a pKa of 4.1; thus, the Essential
$pH = 4.1 + 0.7 \geqq 4.8$
Examples of buffers that produce a solution with pH 4.8 or greater and produce the Essential Buffering Capacity include, but are not limited to, sodium bicarbonate, sodium carbonate, dibasic sodium phosphate, and dipotassium phosphate.
Enough powder for 11 tablets is weighed out:

Proton pump inhibitor:	
Lansoprazole powder	330 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	5500 mg
Dibasic sodium phosphate	2200 mg

The resultant powder is thoroughly mixed. Then 720 mg of the homogeneous mixture is poured into a tablet reservoir (½ inch diameter) and pressed through a full motion of the press as is known in the art. The resultant tablet contains:

Lansoprazole	30 mg
Sodium bicarbonate USP	500 mg
Disodium hydrogen phosphate	200 mg

The tablet contains 6 mEq sodium bicarbonate and 1.4 mEq dibasic sodium phosphate. Variations in this tablet may include a tablet containing all dibasic sodium phosphate or all sodium bicarbonate or other buffers from the Essential Buffers list. The amount of Effective Buffer Capacity per tablet may range from as little as about 4 mEq to as much as about 30 mEq.

Additional tablet disintegrants such as croscarmelose sodium, pregelatinized starch, or providone, and tablet binders such as tapioca, gelatin, or PVP may be added. Further, a film coating may be placed on the tablet to reduce the penetration of light and improve ease of swallowing.

Formulation 17: One Phase Omeprazole 20 mg Tablet Omeprazole has a pKa of 3.9; thus, the Essential pH = 3.9 + 0.7 ≧ 4.6 Examples of buffers that are soluble at pH 4.6 or greater include, but are not limited to, sodium bicarbonate, sodium carbonate, disodium hydrogen phosphate (dibasic sodium phosphate), and dipotassium phosphate. Enough powder for 11 tablets is weighed out:	
Proton pump inhibitor:	
Omeprazole powder USP	220 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	6500 mg
Magnesium oxide powder	1650 mg
Croscarmelose sodium	300 mg

The resultant powder is thoroughly mixed. Then 788 mg of the homogeneous mixture is poured into a tablet reservoir (½ inch diameter) and pressed through a fall motion of the press as is known in the art. The resultant tablet contains:

Omeprazole USP	20 mg
Sodium bicarbonate USP	590 mg
Magnesium oxide	150 mg
Croscarmelose sodium	27.27 mg

The tablet contains 7 mEq sodium bicarbonate and 3.75 mEq magnesium oxide. The amount of Effective Buffer Capacity may range from as little as about 4 mEq to as much as about 30 mEq. The tablet excipients, tablet binders, and film coating of Formulation 16 may also be added.

Formulation 18: One Phase Omeprazole 40 mg Tablet		
Enough powder for 11 tablets is weighed out:		
Proton pump inhibitor:		
Omeprazole powder USP	440	mg
Primary Essential Buffer(s):		
Sodium bicarbonate USP	6500	mg
Magnesium oxide	1650	mg
Pregelatinized starch	500	mg

The resultant powder is thoroughly mixed. Then 826 mg of the homogeneous mixture is poured into a tablet reservoir (½ inch diameter) and pressed through a full motion of the press as is known in the art. The resultant tablet contains:

Omeprazole USP	40 mg
Sodium bicarbonate USP	590 mg
Magnesium oxide	150 mg
Pregelatinized starch	45.45 mg

The tablet contains 7 mEq sodium bicarbonate and 3.75 mEq magnesium oxide. The amount of Effective Buffer Capacity may range from as little as 4 mEq to as much as 30 mEq. The tablet excipients, tablet binders, and film coating of Formulation 16 may also be added.

Esomeprazole magnesium or other proton pump inhibiting agents which are of low solubility (such as the base forms) may be used in place of omeprazole or lansoprazole in the above formulations. The tablet excipients, tablet binders, and film coatings of Formulation 16 may also be added. In addition, powders of any of the formulations disclosed herein may be manufactured by thoroughly mixing the powders as when making tablets and omitting the pressing of the tablets. The powder is packaged in a suitable container protecting the formulation from air moisture and light such as a foil pack or sachet. When added to a volume of water (e.g. 3 to 20 mL) the formulation may be taken orally or administered down a feeding or NG tube, etc. Flavoring agents such as are outlined in the above formulations may be used, for example, carmel flavor 0.1% w/w. For bitter tasting proton pump inhibiting agents such as pantoprazole, omeprazole, esomperazole and rabeprazole, the use of thaumatin in a quantity of 5 to 10 ppm may be useful in masking the bitterness. Sweeteners such as sucrose or aspartame may also be employed. Tablet disintegrants such as croscarmelose sodium and glidants such as magnesium stearate may additionally be used.

Formulation 19: Omeprazole Powder Formulations (single dose)	
Proton pump inhibitor:	
Omeprazole powder USP (or esomeprazole magnesium).	20 mg or 40 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP powder (60 micron)	1000 mg
Magnesium oxide USP powder	500 mg
Optional Secondary Essential Buffer(s):	
Tribasic sodium phosphate	200 mg*
Other ingredients:	
Dextrose	60 mg
Xanthan gum (Rhodigel ultra fine)	15 mg
Thaumatin (Flavor enhancer)	5 to 10 ppm

Thoroughly blend the powder, reconstitute all of the powder with 5 ml to 20 ml distilled water and administer the suspension enterally to the patient.

Formulation 20: Unflavored Omeprazole Powder (single dose)	
Omeprazole powder USP	20 mg or 40 mg
Sodium bicarbonate USP	1500 mg
Parietal cell activator:	
Calcium chloride	200 mg
Other ingredients:	
Dextrose	60 mg
Xanthan gum (Rhodigel ulta fine)	15 mg
Thaumatin (Flavor enhancer)	5 to 10 ppm

Thoroughly blend the powder. Reconstitute all of the powder with 5 mL to 20 mL distilled water and administer the suspension enterally to the patient.

Formulation 21: Flavored Omeprazole Powder (single dose)	
Omeprazole powder USP	20 mg
Dibasic sodium Phosphate duohydrate	2000 mg
Sodium bicarbonate USP	840 mg to 1680 mg
Sucrose	2.6 g
Maltodextrin	200 mg
Cocoa processed with alkali*	180 mg

-continued

Formulation 21: Flavored Omeprazole Powder (single dose)	
Corn syrup solids	600 mg
Xanthan gum	15 mg
Aspartame	15 mg
Thaumatin	2 mg
Soy lecithin	10 mg

*Parietal cell activator

Thoroughly blend the powder. Reconstitute all of the powder with 10 mL to 20 mL distilled water at the time of use.

Formulation 22: Unflavored Lansoprazole Powder (single dose)	
Lansoprazole powder USP	15 mg or 50 mg
Sodium bicarbonate USP	400 mg to 1500 mg

Optionally: Tribasic sodium phosphate to adjust pH for longer stability and enhanced buffering capacity (alternatively other Essential Buffers may be employed)

Thoroughly blend the powder. Reconstitute all of the powder with 5 mL to 20 mL distilled water at the time of use.

Formulation 23: Flavored Lansoprazole Powder (single dose)	
Proton pump inhibitor:	
Lansoprazole powder USP	30 mg
Primary Essential Buffer(s):	
Dibasic Sodium Phosphate USP or Sodium bicarbonate USP	1500 mg
Sucrose	26 g
Maltodextrin	2 g
Cocoa processed with alkali*	18 mg
Corn syrup solids	600 mg
Soy lecithin	80 mg

*Parietal cell activator

Thoroughly blend the powder. Reconstitute all of the powder with 5 mL to 20 mL distilled water at the time of use.

Formulation 24: Unflavored Rabeprazole Powder (single dose)	
Proton pump inhibitor:	
Rabeprazole sodium powder USP	20 mg
Primary Essential Buffer(s):	
Disodium phosphate duohydrate USP	2000 mg
Optional Secondary Essential Buffer(s)	
Tribasic sodium phosphate	100 mg

Thoroughly blend the powder and reconstitute with distilled water prior to administration. Optionally, thickeners and flavoring agents may be added as stated throughout this application. The anticipated volume for this powder would be 20 mL per dose. This formulation is designed to enhance stability of rabeprazole through the use of the common ion effect whereby sodium causes a "salting out" of rabeprazole sodium. This causes the rabeprazole sodium to remain insoluble thereby increasing its stability.

Formulation 25: Unflavored Rabeprazole Powder (single dose)	
Proton pump inhibitor:	
Rabeprazole sodium powder USP	20 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	1200 mg
Secondary Essential Buffer(s):	
Trisodium phosphate USP	300 mg
Optional Secondary Essential Buffer(s):	

Sodium hydroxide or Tribasic potassium may be added in higher or lower amounts to adjust pH for desired stability and additive antacid or buffering capacity.

Thoroughly blend the powder and reconstitute with 15 mL distilled water at the time of use.

Alternatively, a two part product may be employed comprising one part of about 5 to about 15 mL distilled water with a low concentration of Secondary Essential Buffer (e.g. trisodium phosphate (100 mg) or sodium hydroxide (50 mg)) used to dissolve an enteric-coated tablet of rabeprazole thereby producing a stable solution/suspension. This highly alkaline suspension containing low neutralization capacity and rabeprazole sodium may then be added with a second part containing the Primary Essential Buffer(s) having significant neutralization capacity. If desired other Secondary Essential Buffer(s) may be included with the Primary Essential Buffers. This formulation is designed to enable the use of the commercially available enteric-coated tablet of rabeprazole as the source of the proton pump inhibitor. This tablet requires disintegration prior to use as a liquid formulation. Part 1 (the low concentration of Secondary Essential Buffer) produces rapid dissolution of the delayed-release tablet as well as prolonged stability of rabeprazole sodium in the liquid form. This enables the preparation to be prepared prior to administration and simply added to the Primary Essential Buffer(s) (part 2) prior to use.

Formulation 26: Unflavored Rabeprazole Powder (single dose)	
Proton pump inhibitor:	
Rabeprazole sodium powder USP	20 mg
Primary Essential Buffer(s):	
Calcium lactate USP	700 mg
Calcium glycerophosphate	700 mg
Secondary Essential Buffer(s):	
Calcium hydroxide USP	15 mg

(Other Secondary Essential Buffers with cations of sodium or potassium may be added in higher orlower amounts to adjust pH for desirable stability.)

Thoroughly blend the powder. Reconstitute the powder with a liquid part comprising 10 mL glycerol and 10 mL distilled water at the time of use. Alternatively, the liquid for reconstitution may be only water (e.g. distilled) and contain some of the buffer. The liquid for reconstitution may be supplied as a buffered product (to pH 9–11) for dissolving rabeprazole sodium delayed-release tablets (if used as a source of rabeprazole sodium).

Formulation 27: Unflavored Esomeprazole Powder (single dose)	
Proton pump inhibitor:	
Esomeprazole magnesium powder USP	20 mg
Primary Essential Buffer(s):	
Calcium lactate USP	800 mg
Calcium glycerophosphate	800 mg
Secondary Essential Buffer(s):	
Calcium hydroxide USP	15 mg

(Other Secondary Essential Buffers with cations of calcium or magnesium may be added in higher or lower amounts to adjust pH for desirable stability.)

Thoroughly blend the powder. Reconstitute the powder with a liquid part comprising of 10 mL distilled water at the time of use. The liquid for reconstitution may be supplied as a buffered product (to pH 8–11) for dissolving esomeprazole magnesium delayed release granules (if used as a source of esomeprazole magnesium).

Formulation 28: Omeprazole Two Part Tablet Two part tablets contain an outer buffer phase and inner buffer/Proton pump inhibitor core. Enough for 6 tablets is weighed out.	
Inner Core:	
Proton pump inhibitor:	
Omeprazole powder USP (or esomeprazole magnesium or omeprazole sodium).	120 mg
Primary Essential Buffer(s):	
Sodium bicarbonate USP	1200 mg
Outer Phase:	
Sodium bicarbonate USP	3960 mg

(Secondary Essential Buffers such as trisodium phosphate, tripotassium phosphate or sodium carbonate or others may be added to enhance neutralization capacity.)

Thoroughly blend the powders for the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of ⅜" diameter. The powder mixture is then formulated into small tablets by conventional pharmaceutical procedures. Repeat for five additional tablets, then set these small inner tablets aside.

The outside layer surrounding the proton pump inhibitor tablet serves as a pH-buffering zone. Enough sodium bicarbonate for 6 tablets is weighed out with approximately 280 mg per 15 tablet for a total of 1680 mg sodium bicarbonate USP. Then weigh out approximately 280 mg of the resultant blend and add to a die of ½" diameter. Press through a full motion to compact the powder into a tablet. Place the tablet back into the ½ inch die and then place the smaller ⅜" tablet (inner tablet) on top of the ½" tablet and center it. Add approximately 380 mg sodium bicarbonate to the die on top of the ½" tablet and the ⅜" tablet. Press through a full motion to compact the materials into one tablet. The approximate weight of each tablet is 815 mg to 890 mg containing 20 mg omeprazole. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch may be added. The outer lay may also comprise pharmaceutically acceptable tablet exipients. Optional coatings can also be employed, for example, light film coatings and coatings to repel ultraviolet light as is known in the art.

Magnesium oxide or magnesium hydroxide may be substituted for the sodium bicarbonate outer phase. Enough magnesium oxide for 6 tablets is weighed out with approximately 280 mg per tablet for a total of 1680 mg magnesium oxide USP. Then weigh out approximately 280 mg of the resultant blend and add to a die of ½" diameter. Press through a full motion to compact the powder into a tablet. Place the tablet back into the ½ inch die and then place the smaller ⅜" tablet (inner tablet) on top of the ½" tablet and center it. Add approximately 380 mg magnesium oxide to the die on top of the ½" tablet and the ⅜" tablet. Press through a full motion to compact the materials into one tablet. The approximate weight of each tablet is 815 mg to 890 mg containing 20 mg omeprazole. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch, croscarmelose sodium or microcrystalline cellulose (MCC) and colloidal silicone dioxide (CSD) may be added. The outer layer may also comprise pharmaceutically acceptable tablet exipients. Optional coatings can also be employed, for example, light film coatings and coatings to repel ultraviolet light as is known in the art.

The outer phase can alternatively comprise a combination of sodium bicarbonate and magnesium oxide.

Formulation 29: Lansoprazole Two Part Tablet Enough for 6 tablets is weighed out.	
Inner Core:	
Proton pump inhibitor:	
Lansoprazole powder USP	180 mg
Primary Essential Buffer:	
Sodium bicarbonate USP	1200 mg
Outer Phase:	
Sodium bicarbonate USP	3960 mg

Thoroughly blend the powders of the inner core, then weigh out approximately 230 mg of the resultant blend and add to a die of ⅜" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 825 mg to 900 mg. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch may be added.

Formulation 30: Pantoprazole Two Part Tablet Enough for 6 tablets is weighed out.	
Inner Core:	
Proton pump inhibitor:	
Pantoprazole powder USP (or pantoprazole sodium)	240 mg
Primary Essential Buffer:	
Sodium bicarbonate USP	1200 mg
Outer Phase:	
Sodium bicarbonate USP	3960 mg

Thoroughly blend the powders for the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of ⅜" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 835 mg to 910 mg. Binders such as tapioca or PVP and disintigrants such as pregelatinized starch or croscarmelose sodium may be added.

Formulation 31: Omeprazole or esomeprazole two part tablet. Enough for 6 tablets is weighed out.	
Inner Core:	
Proton pump inhibitor:	
Omeprazole powder USP (or esomeprazole or omeprazole sodium).	120 mg
Primary Essential Buffer:	
Sodium bicarbonate	1200 mg
Outer Phase:	
Sodium bicarbonate	3960 mg

Thoroughly blend the powders of the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of ⅜" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 815 mg to 890 mg. Binders such as tapioca or PVP and disintigrants have been mentioned and may be added. Secondary Essential Buffers such as trisodium phosphate, tripotassium phosphate or sodium carbonate or others may be added to enhance neutralization capacity.

Formulation 32: Lansoprazole Two part tablet Enough for 6 tablets is weighed out.	
Inner Core:	
Proton pump inhibitor:	
Lansoprazole powder USP	180 mg
Primary Essential Buffer:	
Sodium bicarbonate	1200 mg
Outer Phase:	
Sodium bicarbonate	3960 mg

Thoroughly blend the powder of the inner core, then weigh out approximately 230 mg of the resultant blend and add to a die of ⅜" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 825 mg to 900 mg. Binders such as tapioca or PVP and disintigrants have been mentioned and may be added. Secondary Essential Buffers such as trisodium phosphate, tripotassium phosphate or sodium carbonate or others may be added to enhance neutralization capacity.

Formulation 33: Pantoprazole Two part tablet Enough for 6 tablets is weighed out.	
Inner Core:	
Proton pump inhibitor:	
Pantoprazole sodium powder USP	240 mg
Primary Essential Buffer:	
Sodium bicarbonate	1200 mg
Outer Phase:	
Sodium bicarbonate	3960 mg

Thoroughly blend the powders of the inner core, then weigh out approximately 220 mg of the resultant blend and add to a die of ⅜" diameter. The inner and outer tablets are then formed as described in Formulation 28. The approximate weight of each tablet is 835 mg to 910 mg. Binders such as tapioca or PVP and disintegrants may also be added. Secondary Essential Buffers, such as trisodium phosphate, tripotassium phosphate, sodium carbonate or others, may be added to enhance neutralization capacity.

Formulation 34: Omeprazole 20 mg Two-Part Tablet	
Inner Core:	
Proton pump inhibitor:	
Omeprazole enteric coated granules (base, or sodium salt or esomeprazole sodium or magnesium)	20 mg
Outer Phase:	
Sodium bicarbonate powder USP	1000 mg

The inner core is created as is known in the art such that the enteric coatings on the granules remain substantially intact. The outer phase is bound to the inner core as described in Formulation 28. Other variations of this tablet include a uniform enteric coating surrounding the proton pump inhibitor of the inner core instead of separate enteric coated granules.

Formulation 35: Lansoprazole 30 mg Two-Part Tablet	
Inner Core:	
Proton pump inhibitor:	
Lansoprazole enteric coated granules	30 mg
Outer Phase:	
Sodium bicarbonate powder USP	1000 mg

This two-part tablet is formulated as per Formulation 34.

Formulation 36: Rabeprazole 20 mg Two-Part Tablet	
Inner Core:	
Proton pump inhibitor:	
Rabeprazole enteric coated granules	20 mg
Outer Phase:	
Sodium bicarbonate powder USP	1000 mg

This two-part tablet is formulated as per Formulation 34.

Formulation 37: Omeprazole Two Part Tablet Enough for 6 tablets is weighed out	
Inner Core:	
Omeprazole	120 mg
Sodium bicarbonate power USP	1200 mg
Outer Phase:	
Magnesium oxide	1500 mg
Optional - calcium carbonate	3000 mg

The omeprazole and sodium bicarbonate of the inner core are homogeneously mixed and formed as in Formulation 28. The outer phase is combined with the inner core as in Formulation 28.

Formulation 38: Combination Antacid and Enteric Coated Dosage Form	
Omeprazole enteric coated granules or enteric coated tablet	20 mg (or an equivalent dose of another proton pump inhibitor)
Calcium carbonate	1000 mg

The above components are combined with care exerted to ensure that the enteric coating is not crushed or otherwise compromised. The resulting combination is then formed into compressed tablets or placed in capsules as is known in the pharmaceutical art. If enteric coated granules are employed, they are generally, but not required, dispersed throughout the tablet or capsule. If an enteric coated tablet is alternatively utilized, it forms a central core, which is uniformly surrounded by the calcium carbonate in either a compressed tablet or in a larger capsule. In another embodiment, a capsule containing enteric coated granules of proton pump inhibitor can be placed within a larger capsule containing the calcium carbonate.

It should be noted that other buffering agents can be utilized in lieu of or in combination with calcium carbonate. The buffer(s) employed is present in an amount of at least about 5 mEq per dose of the composition with the preferred range been 7.5 to 15 mEq. For example, sodium bicarbonate may be preferred over calcium carbonate and other antacids (such as magnesium or aluminum salts) because in many cases, sodium bicarbonate more quickly lowers gastric pH.

Formulation 39: Combination Rapid Release and Delayed Released Proton Pump Inhibitor and Antacid	
Inner core:	
Omeprazole enteric coated granules or enteric coated tablet	10 or 20 mg (or an equivalent dose of another proton pump inhibitor)
Outer phase:	
Omeprazole powder	10 or 20 mg (or equivalent dose of another proton pump inhibitor)
Calcium Carbonate powder	1000 mg

The constituents of the outer phase are uniformly mixed. The inner core is created as is known in the art such that the enteric coatings on the granules or tablet remain substantially intact. The outer phase is bound to the inner core as described herein and as known in the art.

Formulation 40: Soft Chewable Proton Pump Inhibitor—Buffer Dosage Form

Omeprazole 10 or 20 mg (or an equivalent dose of another proton pump inhibitor) is combined with the ingredients of a soft chewable antacid tablet (e.g., Viactiv®), which comprises calcium carbonate 500 or 1000 mg, corn syrup, sugar, chocolate non fat milk, cocoa butter, salt, soy lecithin, glyceryl monostearate, flavoring (e.g., caramel), carrageenan, and sodium phosphate. Vitamins D3 and/or K1 can also be added. The finished chew tablets are administered to patients once to thrice daily for gastric acid related disorders.

For all formulations herein, multiple doses may be proportionally compounded as is known in the art.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation. All patents and other references cited herein are incorporated herein by reference in their entirety. Obviously, many modifications, equivalents, and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described.

I claim:

1. A method of treating a gastric acid related disorder in a subject in need thereof, comprising:

providing a solid pharmaceutical composition for oral administration to the subject, the composition consisting essentially of: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H^+, K^+-ATPase proton pump inhibitor; (b) at least one buffering agent in an amount of about 0.1 mEq to about 2.5 mEq per mg proton pump inhibitor; and (c) one or more optional pharmaceutically acceptable excipients; and

orally administering the pharmaceutical composition to the subject,

wherein upon oral administration of the pharmaceutical composition to the subject, an initial serum concentration of the proton pump inhibitor greater than about 0.1 μg/ml is obtained at any time within about 30 minutes after administration of the composition.

2. The method of claim 1, wherein the composition is administered in an amount to achieve an initial serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml at any time within about 30 minutes after administration of the composition.

3. The method of claim 1, wherein the pharmaceutical composition is in a form selected from the group consisting of a tablet, capsule, powder, suspension tablet, effervescent tablet or capsule, chewable tablet, granules, pellets, and a liquid created by mixing any of the foregoing with an aqueous medium.

4. The method of claim 1, wherein the amount of the proton pump inhibitor absorbed into the serum is therapeutically effective in treating the gastric acid related disorder selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, heartburn, esophageal disorder, and acid dyspepsia.

5. The method of claim 1, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, tautomer, ester, amide, derivative, prodrug, free base, or salt thereof.

6. The method of claim 1, wherein the amount of the proton pump inhibitor is about 2 mg to about 300 mg.

7. The method of claim 1, wherein the amount of the proton pump inhibitor is about 10 mg to about 120 mg.

8. The method of claim 1, wherein the amount of the proton pump inhibitor is about 2 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, a 115 mg, or about 120 mg.

9. The method of claim 1, wherein the amount of the buffering agent is about 10 mEq to about 70 mEq.

10. The method of claim 1, wherein the amount of the buffering agent is at least 10 mEq.

11. The method of claim 1, wherein the amount of the buffering agent is about 15 mEq to about 55 mEq.

12. The method of claim 1, wherein the buffering agent comprises a combination of calcium carbonate and sodium bicarbonate.

13. The method of claim 1, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

14. The method of claim 1, wherein the buffering agent is selected from the group consisting of a bicarbonate salt of a Group IA metal, an alkali earth metal buffering agent, a calcium buffering agent, a magnesium buffering agent, an aluminum buffering agent, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium aluminate, magnesium carbonate, magnesium silicate, magnesium citrate, aluminum hydroxide, aluminum phosphate, aluminum hydroxide/magnesium carbonate, potassium carbonate, potassium citrate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, aluminum magnesium hydroxide, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, sodium dihydrogen phosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, potassium metaphosphate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium gluconate, calcium bicarbonate, calcium citrate, calcium phosphate magnesium phosphate, potassium phosphate, sodium phosphate, trihydroxymethylaminomethane, an amino acid, an acid salt of an amino acid, an alkali salt of an amino acid, and combinations of any of the foregoing.

15. The method of claim 1, wherein the buffering agent comprises sodium bicarbonate.

16. The method of claim 15, wherein the sodium bicarbonate is in an amount from about 250 mg to about 4000 mg.

17. The method of claim 15, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 2000 mg.

18. The method of claim 15, wherein the sodium bicarbonate is in an amount of at least about 400 mg.

19. The method of claim 1, wherein the buffering agent comprises calcium carbonate.

20. The method of claim 19, wherein the calcium carbonate is in an amount from about 250 mg to about 4000 mg.

21. The method of claim 19, wherein the calcium carbonate is in an amount from about 1000 mg to about 2000 mg.

22. The method of claim 19, wherein the calcium carbonate is in an amount of at least about 400 mg.

23. The method of claim 1, wherein the excipient is selected from the group consisting of a pharmaceutically compatible carrier, a binder, a suspending agent, a flavoring agent, a sweetening agent, a disintegrant, a flow aid, a lubricant, an adjuvant, a colorant, a diluent, a moistening agent, a preservative, a parietal cell activator, an anti-foaming agent, an antioxidant, a chelating agent, an antifungal agent, an antibacterial agent, e* an isotonic agent, and combinations of any of the foregoing.

24. The method of claim 1, wherein the excipient is one or more flavoring agents selected from the group consisting of aspartame, thaumatin, sucrose, dextrose, or a chocolate, a cocoa, a cola, a peppermint, a spearmint, a watermelon, an apple, a caramel, a meat, a root beer, a maple, a cherry, a coffee, a mint, a licorice, a nut, a butter, a butterscotch, a butter pecan, or a peanut butter flavoring, and combinations of any of the foregoing.

25. The method of claim 1, wherein the composition is administered once or twice a day.

26. A method of treating a gastric acid related disorder in a subject in need thereof, comprising:

orally administering to the subject a single dose of a solution or suspension of a pharmaceutical composition, the composition consisting essentially of: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H^+, K^+-ATPase proton pump inhibitor; (b) at least one buffering agent in an amount of about 0.1 mEq to about 2.5 mEq per mg proton pump inhibitor; and (c) one or more optional pharmaceutically acceptable excipients wherein an initial serum concentration of the proton pump inhibitor greater than about 0.1 μg/ml is obtained at any time within about 30 minutes after administration of the composition, and wherein the administering step does not require further administration of the buffering agent (s) beyond that administered in the single dose.

27. The method of claim 26, wherein the composition is administered in an amount to achieve an initial serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml at any time within about 30 minutes after administration of the composition.

28. The method of claim 26, wherein the subject is fasting.

29. The method of claim 26, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, tautomer, ester, amide, derivative, prodrug, free base, or salt thereof.

30. The method of claim 26, wherein the amount of the proton pump inhibitor is about 2 mg to about 300 mg.

31. The method of claim 26, wherein the amount of the proton pump inhibitor is about 10 mg to about 120 mg.

32. The method of claim 26, wherein the amount of the proton pump inhibitor is about 2 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 rug, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 rug, about 100 mg, about 105 mg, about 110 mg, about 15 mg, or about 120 mg.

33. The method of claim 26, wherein the amount of the buffering agent is about 10 mEq to about 70 mEq.

34. The method of claim 26, wherein the amount of the buffering agent is at least 10 mEq.

35. The method of claim 26, wherein the amount of the buffering agent is about 15 mEq to about 55 mEq.

36. The method of claim 26, wherein the buffering agent comprises a combination of calcium carbonate and sodium bicarbonate.

37. The method of claim 26, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

38. The method of claim 26, wherein the buffering agent is selected from the group consisting of a bicarbonate salt of a Group IA metal, an alkali earth metal buffering agent, a calcium buffering agent, a magnesium buffering agent, an aluminum buffering agent, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium aluminate, magnesium carbonate, magnesium silicate, magnesium citrate, aluminum hydroxide, aluminum phosphate, aluminum hydroxide/magnesium carbonate, potassium carbonate, potassium citrate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, aluminum magnesium hydroxide, sodium citrate, sodium tartrate,

sodium acetate, sodium carbonate, sodium (polyphosphate, sodium dihydrogen phosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, potassium metaphosphate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium gluconate, calcium bicarbonate, calcium citrate, calcium phosphate magnesium phosphate, potassium phosphate, sodium phosphate, trihydroxymethylaminomethane, ail amino acid, an acid salt of an amino acid, an alkali salt of an amino acid, and combinations of any of the foregoing.

39. The method of claim 26, wherein the buffering agent comprises sodium bicarbonate.

40.The method of claim 39, wherein the sodium bicarbonate is in an amount from about 250 mg to about 4000 mg.

41. The method of claim 39, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 2000 mg.

42. The method of claim 39, wherein the sodium bicarbonate is in an amount of at least about 400 mg.

43. The method of claim 39, wherein the buffering agent comprises calcium carbonate.

44. The method of claim 43, wherein the calcium carbonate is in an amount from about 250 mg to about 4000 mg.

45. The method of claim 43, wherein the calcium carbonate is in an amount from about 1000 mg to about 2000 mg.

46. The method of claim 43, wherein the calcium carbonate is in an amount of at least about 400 mg.

47. The method of claim 26, wherein the excipient is selected from the group consisting of a pharmaceutically compatible carrier, a binder, a suspending agent, a flavoring agent, a sweetening agent, a disintegrant, a flow aid, a lubricant, an adjuvant, a colorant, a diluent, a moistening agent, a preservative, a parietal cell activator, an anti-foaming agent, an antioxidant, a chelating agent, an antifungal agent, an antibacterial agent, or an isotonic agent, and combinations of any of the foregoing.

48. The method of claim 26, wherein the subject is an adult human.

49. The method of claim 26, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, heartburn, esophageal disorder, and acid dyspepsia.

50. The method of claim 26, wherein the excipient is one or more flavoring agents selected from the group consisting of aspartame, thaumatin, sucrose, dextrose, or a chocolate, a cocoa, a cola, a peppermint, a spearmint, a watermelon, an apple, a caramel, a meat, a root beer, a maple, a cherry, a coffee, a mint, a licorice, a nut, a butter, a butterscotch, a butter pecan, or a peanut butter flavoring, and combinations of any of the foregoing.

51. The method of claim 26, wherein the composition is administered once or twice a day.

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Sodium Bicarbonate for the Treatment of Lactic Acidosis*

Sean M. Forsythe, MD; and Gregory A. Schmidt, MD, FCCP

Lactic acidosis often challenges the intensivist and is associated with a strikingly high mortality. Treatment involves discerning and correcting its underlying cause, ensuring adequate oxygen delivery to tissues, reducing oxygen demand through sedation and mechanical ventilation, and (most controversially) attempting to alkalinize the blood with IV sodium bicarbonate. Here we review the literature to answer the following questions: Is a low pH bad? Can sodium bicarbonate raise the pH *in vivo*? Does increasing the blood pH with sodium bicarbonate have any salutary effects? Does sodium bicarbonate have negative side effects? We find that the oft-cited rationale for bicarbonate use, that it might ameliorate the hemodynamic depression of metabolic acidemia, has been disproved convincingly. Further, given the lack of evidence supporting its use, we cannot condone bicarbonate administration for patients with lactic acidosis, regardless of the degree of acidemia. *(CHEST 2000; 117:260–267)*

Key words: acid-base; acidosis; alkalinizing therapy; bicarbonate; lactic acidosis; sodium bicarbonate

Abbreviations: DCA = dichloroacetate; DKA = diabetic ketoacidosis; SID = strong ion difference

Lactic acidosis, defined as a lactate concentration > 5 mmol/L and a pH < 7.35, commonly complicates critical illness. Its causes are legion, including sepsis, cardiogenic shock, severe hypoxemia, hepatic failure, and intoxication. Many of these share reduced delivery of oxygen to cells or impaired use of oxygen in mitochondria, yet some are based in more complex derangements. For example, the lactic acidosis of sepsis is poorly understood but probably cannot be explained simply by tissue hypoxia, at least at the level of the whole body. Treatment of lactic acidosis involves discerning and correcting its underlying cause, ensuring adequate oxygen delivery to tissues, reducing oxygen demand through sedation and mechanical ventilation, and (in some ICUs) attempting to alkalinize the blood with IV sodium bicarbonate. Even in the face of maximal supportive therapy, lactic acidosis is associated with a mortality of 60 to 90%.[1–4]

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Although the use of sodium bicarbonate for the treatment of metabolic acidosis has been debated most heavily in the past 15 years, its use was questioned as far back as 1934.[5] Nevertheless, it is still considered standard therapy and recommended in many textbooks and review articles,[6–8] despite the lack of relevant clinical data supporting its effectiveness. Here we review the animal and human studies that bear on this complex, yet common, clinical conundrum.

We will not address the use of sodium bicarbonate in the bicarbonate-losing metabolic acidoses, such as those caused by diarrhea or renal tubular acidosis, in which replacement of lost bicarbonate is widely accepted. Although we touch on the use of bicarbonate in diabetic ketoacidosis (DKA) and some other forms of metabolic acidosis, our discussion and conclusions largely relate to the single most common cause of severe lactic acidosis in the modern ICU, that caused by severe sepsis.[4] We find little evidence that sodium bicarbonate is detrimental in these conditions, but its use fails the most basic criteria expected of any drug–efficacy.

Those who continue to advocate the use of sodium bicarbonate for lactic acidosis generally use the following chain of reasoning (explicitly or implicitly):

1. A low pH, in and of itself, is harmful (most notably by impairing cardiovascular function).
2. Sodium bicarbonate can increase the pH when infused IV.
3. Raising the pH with sodium bicarbonate improves cardiovascular function or some other relevant outcome.
4. Any adverse effects of sodium bicarbonate are outweighed by its benefits.

We address below each of these points in turn.

Is a Low pH Bad?

Proteins, which underlie the function and structure of human cells, contain areas of both positive and negative charge and are thereby sensitive to the pH of the surrounding milieu. One can conceive of innumerable ways in which excess acid could impair protein function and, by extension, the function of the whole body. Yet it is overly simplistic to assume that the clinician's window on acid-base state, the arterial blood pH, reflects accurately the pH at a (likely more important) cellular level. For example, a 50% reduction in blood flow to a tissue causes the arterial-venous P_{CO_2} difference to double (as long as CO_2 production and excretion remain constant) as predicted by the Fick principle. This will substantially raise the tissue P_{CO_2} and lower the local intracellular pH. At the same time, neither the arterial pH nor P_{CO_2} changes at all, both failing completely to reveal the tissue acidosis. Further clouding the value of the arterial blood pH, there may be different acid-base states in different cells of a single organ, or within different organs of a single patient. Mitochondrial pH may be even more crucial than cellular (cytoplasmic) pH, as these organelles are the site of energy production. In experiments involving isolated rat hepatocytes, the mitochondrial membrane pH gradient did not change when extracellular pH was lowered from 7.40 to 6.9.[9]

Because adults with acidosis generally also have sepsis, hypoxemia, intoxication, or hypoperfusion, discerning the physiologic effects of low pH from those of endotoxemia, hypoxemia, and so on is a challenging task. In isolated animal heart muscle preparations in which the pH of the perfusate is lowered, acidosis generally reduces contractile function,[10] sometimes severely.[11] Human ventricular muscle excised during open-heart surgery displays only modestly reduced contractility in the face of severe acidosis.[12] The cardiac depressant effect may be caused by inorganic phosphate-mediated impairment of actin-myosin crossbridge cycling, disruption of energy production,[11,13] interference with calcium delivery to myofilaments, or decreased sensitivity of contractile proteins to calcium.[14] In whole-animal preparations, the effects of acidosis are more difficult to discern, because of competing effects of acidosis on contractility, heart rate, vascular tone, and the adrenal and sympathetic systems. Various investigators have controlled heart rate, preload, and afterload, finding that acidosis caused contractility to remain constant,[15] decrease marginally,[16] or transiently rise and then fall.[17]

The increasing experience with permissive hypercapnia for patients with ARDS or status asthmaticus, in which hypercapnia and acidemia are tolerated to avoid alveolar overdistention, has changed many clinicians' perspective about the adverse impact of acidemia. In sedated and ventilated patients with ARDS, rapid intentional hypoventilation (pH falling from 7.40 to 7.26 in 30 to 60 min) lowered systemic vascular resistance while cardiac output rose. Mean systemic arterial pressure and pulmonary vascular resistance were unchanged.[18] Further, in many studies of patients undergoing permissive hypercapnia, a pH of well below 7.2 was tolerated well,[18–25] as it is in young patients with DKA,[26] children with "supercarbia,"[27] and those with grand mal seizures.[28–30] The feared consequences of acidemia, projected from the experience with patients having lactic acidosis (and, usually, concomitant sepsis), failed to materialize. In normal subjects who rebreathed carbon dioxide, QT dispersion was increased, which could signal a risk of arrhythmia.[24] With data now available for many patients permissively hypoventilated, the systemic hemodynamic effects are quite small even as the pH falls to 7.15, with the typical patient experiencing no change or small increases in cardiac output and BP. Rhythm disturbances have not been a problem. Patients whose pH levels fall far below 7.0 are fewer in number, so firm conclusions cannot be drawn, but they similarly tolerate their acidemia. The current practice of permissive hypercapnia does not generally include an attempt to alkalinize the blood to compensate for respiratory acidosis.

Cardiac contractile response to catecholamines is also impaired by acidosis, perhaps mediated by a decline in β-receptors on the cell surface.[13,31,32] Other potentially detrimental cardiovascular effects of acidosis include reduced resuscitability from induced ventricular fibrillation, which has been shown in rats but not in dogs or pigs,[33–35] impaired load tolerance of the right ventricle,[36] and altered renal blood flow (both increased and decreased, depending on the degree of acidemia).[37] Diaphragmatic contractility is reduced also by respiratory acidosis,[38] but apparently not by metabolic acidosis.[39]

Paradoxically, acidosis may have protective effects in critical illness. A low pH has been shown to delay

the onset of cell death in isolated hepatocytes exposed to anoxia[9] and to chemical hypoxia.[40] Correcting the pH took away the protective effect and accelerated cell death. In addition, acidosis during reperfusion limits myocardial infarct size.[41,42]

In summary, although a very low pH has negative inotropic effects in isolated hearts, the whole-body response in patients is much less clearly detrimental. Although clinical shock and metabolic acidosis often coincide, the striking discordance between the clinical course and outcome of patients with (usually septic) lactic acidosis compared with those who have DKA or ventilatory failure suggests that the low pH itself does not crucially underpin the hemodynamic collapse of these ill patients. Independent of the acidemia, the lactate ion may be significant, because lactate buffered to a pH of 7.4 can cause decreased cardiac contractility in animal models.[43]

Can Sodium Bicarbonate Raise the pH *In Vivo*?

It seems straightforward that adding a base to acidic blood will raise the pH–the reality is more complex. First, bicarbonate is not one of the independent determinants of the blood pH. Rather, these include the difference between the total concentrations of strong cations and anions (the strong ion difference, [SID]); the total concentration of weak acids; and the Pa_{CO_2}.[44] Administration of exogenous sodium bicarbonate increases the SID (which tends to raise the pH) because sodium is a strong cation and bicarbonate is not a strong ion at all, but at the same time it elevates the Pa_{CO_2} (which tends to lower pH). In patients with lactic acidosis receiving mechanical ventilation, a modest infusion of sodium bicarbonate (2 mmol/kg for 15 min IV) boosted Pa_{CO_2} from 35 to 40 mm Hg.[2]

Second, bicarbonate administration may engender metabolic reactions that may themselves alter (SID), the total concentration of weak acids, or Pa_{CO_2}. For example, in animals and humans, bicarbonate infusion can augment the production of lactic acid, a strong anion.[45–50] Mechanisms to explain this remain speculative, but include a shift in the oxyhemoglobin-saturation relationship[51]; enhanced anaerobic glycolysis, perhaps mediated by the pH-sensitive, rate-limiting enzyme phosphofructokinase; and changes in hepatic blood flow or lactate uptake.[52]

In animal models of lactic acidosis, sodium bicarbonate does not predictably raise the arterial pH. In some studies, pH remained constant or fell.[46,47] Most whole-animal studies, however, have shown that pH can be raised and even normalized.[16,48,49,53–55] Most relevant to clinical practice, in two studies of patients with lactic acidosis receiving mechanical ventilation, IV infusion of sodium bicarbonate in dosages of 2 mmol/kg for 15 min or 1 mmol/kg for 1 to 2 min raised the pH only 0.14 and 0.05 units, respectively.[2,56]

Yet, the body has multiple compartments separated by membranes of differing permeabilities and systems of active transport. Even when sodium bicarbonate added to the central veins reliably elevates the arterial pH, its effects on the cerebrospinal fluid and intracellular spaces may not be concordant. This could happen because carbon dioxide, produced when bicarbonate reacts with metabolic acids, diffuses readily across cell membranes and the blood-brain barrier, whereas bicarbonate cannot. Alternatively, as discussed above, bicarbonate may provoke reactions within cells, vessels, or organs that lower the local SID or raise the local P_{CO_2}.

Sodium bicarbonate lowered cerebrospinal fluid pH in dogs with DKA,[57] dogs being resuscitated after a ventricular fibrillation arrest,[58] and two patients with DKA, in whom it was associated with a decrease in mental status.[59] Intracellular pH has been measured in cells or animals using nuclear magnetic resonance spectroscopy, pH-sensitive fluorescent dyes, intramuscular electrodes, and the distribution of carbon 14-labeled dimethadione (Table 1). The results are inconsistent, with intracellular pH rising in one study,[55] not changing in six studies,[11,34,49,53,60,61] falling in nine studies,[46,47,62–68] and either rising or falling depending on the buffer used in two investigations.[69,70] In various studies, intracellular pH has been shown to fall with bicarbonate in RBCs,[46] muscle,[68] liver,[47] lymphocytes,[66] and brain.[63] We are aware of only one human study involving determination by magnetic resonance spectroscopy of intracellular pH in the brain.[65] When these normal volunteers were given sodium bicarbonate IV, brain pH fell significantly.

In summary, sodium bicarbonate can raise the blood pH when given IV. In contrast, this therapy fails to augment reliably the intracellular pH. Indeed, intracellular pH falls in most animal models and in most organs studied, but the effect is variable.

Does Increasing the Blood pH With Sodium Bicarbonate Have any Salutary Effects?

The most direct question to pose regarding sodium bicarbonate therapy is whether it improves the problems that prompt its use. Namely, does it correct hemodynamics, "buy time" for other interventions, or improve outcome?

In isolated rat or rabbit hearts perfused with acidic solutions, bicarbonate fails to augment ventricular

Table 1—*Results of Studies of the Effect of Bicarbonate on Intracellular pH**

Source	Subject	Acidosis	Method of Measuring Intracellular pH	Serum pH	Intracellular pH
Beech et al.[55]	Rat	DKA, shock	^{31}P NMR	↑	↑ (heart)
Rhee et al.[49]	Dog	Hypoxic lactic	^{31}P NMR	↔	↔ (heart)
Beech et al.[53]	Rat	Hypotensive lactic	C2 NMR	↑	↔ (muscle)
Bollaert et al.[60]	Rat	Septic (LPS)	^{31}P NMR	↑	↔ (muscle)
Shapiro[11]	Rat heart	Acidic perfusate	^{31}P NMR	↑	↔ (heart)
Thompson et al.[61]	Rat	None	^{31}P NMR	↑	↔ or ↓ depending on route (IV or IP)
Kette et al.[34]	Pig	Cardiac arrest	Electrode	↑	↔ (heart)
Arieff et al.[46]	Dog	Phenformin lactic	^{14}C DMO	↔	↓ (liver, RBC)
Graf et al.[47]	Dog	Hypoxic lactic	^{14}C DMO	↔	↓ (liver)
Bersin and Arieff[62]	Dog	Hypoxic lactic	^{14}C DMO	↓	↓ (liver)
Shapiro et al.[63]	Rat	NH_4Cl, hypercapnic	^{31}P NMR	↑	↓ (brain)
Shapiro et al.[64]	Rat	NH_4Cl	^{31}P NMR	↑	↓ (liver)
Arieff et al.[68]	Animal	Phenformin lactic	Not stated	↑	↓ (liver and muscle)
Nakashima et al.[65]	Human	None	^{31}P NMR		↓ (brain)
Bjerneroth et al.[66]	Lymphocytes	Acidic buffer	Fluorescent dye	↑	↓
Ritter et al.[67]	Platelets	Acidic buffer	Fluorescent dye		↓
Levraut et al.[70]	Rat hepatocytes	Acidic buffer	Fluorescent dye		↑ or ↓ depending on buffer
Goldsmith et al.[69]	Leukocytes	Acidic buffer	Fluorescent dye		↑ or ↓ depending on buffer

*NH_4Cl = ammonium chloride; NMR = nuclear magnetic resonance; DMO = dimethyloxazolidine; IP = intraperitoneal; LPS = lipopolysaccharide; ↑ = increase; ↓ = decrease; ↔ = no change.

contractility.[11,71] In whole animals (including various models of metabolic acidosis), the effects of bicarbonate on ventricular function are more difficult to tease out from its impact on systemic vessels. Further, one must take care not to interpret these studies too simplistically. For example, a fall in BP is not necessarily detrimental (if cardiac output rises). Nevertheless, these studies uniformly fail to reveal any hemodynamic benefit for sodium bicarbonate when compared with iso-osmolar saline solution.[16,45–49,53,55,62,64,72–74] When it has been measured, cardiac output either does not change[48,49,74] or falls.[11,46,47] Right ventricular contractility[72,74] and hepatic blood flow[46,47] fall. Perhaps the most careful study of left ventricular function involved L-lactic acid infusion in anesthetized, ventilated, β-blocked, and atrially paced dogs. Before and after bicarbonate infusion, the left ventricular pressure-volume relationship was determined with a ventricular Millar catheter and three orthogonal pairs of ultrasonic crystals imbedded in the ventricular walls.[16] Although sodium bicarbonate increased the arterial pH and did not increase lactate concentrations, mean arterial pressure fell, and cardiac output and ventricular contractility (slope of the end-systolic pressure-volume relationship) did not change. The hemodynamic effects were indistinguishable from those of saline solution.

There have been two studies of the hemodynamic impact of sodium bicarbonate in human lactic acidosis.[2,56] In both studies, patients were receiving mechanical ventilation, had a mean blood lactate between 7 mmol/L and 8 mmol/L, and were receiving continuous infusions of vasoactive drugs (except one patient in one study). Although sodium bicarbonate raised pH and serum bicarbonate concentrations, it did not improve hemodynamics or catecholamine responsiveness. Specifically, bicarbonate was indistinguishable from saline with regard to heart rate, central venous pressure, pulmonary artery pressure, mixed venous oxyhemoglobin saturation, systemic oxygen delivery, oxygen consumption, arterial BP, pulmonary artery occlusion (wedge) pressure, and cardiac output.[2,56] These findings suggest that the commonly observed hemodynamic response to bicarbonate administration in patients treated with vasoactive drug infusions may simply be one of preload augmentation (rather than enhanced catecholamine responsiveness). When the most severely acidemic (pH range 6.9 to 7.2) subset of patients was analyzed separately, these negative findings persisted.[2] This result does not support the practice of some physicians who withhold bicarbonate from patients with mild acidemia but feel compelled to give it to those with acidemia of greater magnitude. Indeed, if there are negative effects of bicarbonate infusion, there are reasons to expect that this subset of patients will suffer disproportionately (*ie*, develop more profound paradoxical intracellular acidosis).

Outcome is difficult to measure because animal models have a nearly 100% mortality and human trials have generally not been designed to detect differences in survival or other (nonhemodynamic) measures of outcome. In both prospective and retrospective studies of patients with DKA treated with or without sodium bicarbonate, there were no dif-

ferences in the neurologic status, incidence of hypokalemia or hypoglycemia, or rate of correction of acidemia,[75,76] but there was a suggestion of delayed clearance of ketones and lactate in patients given bicarbonate.[77,78] Dichloroacetate (DCA) infusion, which, like sodium bicarbonate infusion, effectively raises serum pH in critically ill patients with lactic acidosis (but lowers lactate concentrations), also has no apparent hemodynamic benefit and does not improve survival.[3]

The only study that has shown any positive effect on outcome is in the setting of canine ventricular fibrillation.[79] Dogs resuscitated from prolonged arrest who were given bicarbonate had improved return of the circulation, less neurologic deficit, and greater survival to 24 h. On the other hand, several other studies in both humans and animals do not support these data. A study in dogs showed no effect of respiratory or metabolic acidosis on defibrillation threshold.[35] Sodium bicarbonate had no detectable impact on myocardial cell pH or resuscitability from ventricular fibrillation in pigs in one study[34] and worsened coronary perfusion pressure and resuscitability in yet another.[80] Its use was associated with poorer outcomes in a retrospective study of human cardiopulmonary arrest.[81]

In summary, no controlled study has shown improved hemodynamics attributable to sodium bicarbonate infusion, regardless of the effect on pH, and many show worsening of some hemodynamic variable. It is significant that such negative findings include two studies in critically ill humans receiving infused catecholamines, the subset of patients who might be expected to benefit most dramatically.

Does Sodium Bicarbonate Have Negative Side Effects?

The most obvious side effects of sodium bicarbonate are the fluid and sodium load. This can cause hypervolemia, hyperosmolarity, and hypernatremia.[82] Sodium bicarbonate given as a rapid IV bolus can cause a transient fall in mean arterial pressure and a transient rise in intracranial pressure[83] that is probably related to its hypertonicity, and this is alleviated when given as a slow IV infusion. Sodium bicarbonate has been shown in three studies to lower PaO_2 from 5 to 15 mm Hg in both acidemic animals and nonacidemic patients with congestive heart failure.[57,84] The mechanism for this is unclear, but the authors speculated that there might be worsening of intrapulmonary shunt.

When normal human volunteers were made acidemic with acetazolamide and then corrected with sodium bicarbonate, the acute correction of the pH caused increased hemoglobin affinity for oxygen that worsened oxygen delivery. This effect lasted about 8 h.[51] This was thought to be caused by the immediate nature of the Bohr effect and the delayed nature of the 2,3-diphosphoglycerate effect on hemoglobin-oxygen affinity.

Lactate concentrations increased with sodium bicarbonate infusion (compared with control subjects) in animal studies of hypoxic lactic acidosis,[45,47,49] phenformin-induced lactic acidosis,[46,68] hemorrhagic shock,[48] and DKA.[55,57] This finding has also been reported in cases of chronic lactic acidosis associated with malignancies.[85] It is possible that lactate rises in these settings because of impaired oxygen delivery to tissues. Even if enhanced lactate production does not signal cellular hypoxia, bicarbonate-induced hyperlactatemia may be detrimental inasmuch as lactate itself has potentially detrimental actions, as discussed earlier.

Serum ionized calcium concentration is reduced by sodium bicarbonate infusion. In a randomized, controlled study of ICU patients with lactic acidosis, sodium bicarbonate lowered ionized calcium from 0.95 to 0.87 mmol/L.[2] In an animal study of cardiac arrest, sodium bicarbonate decreased ionized calcium, although this had no apparent detrimental effects.[79] Because left ventricular contractility has been shown to vary directly with ionized calcium concentration,[86] any beneficial effects of pH correction may be masked by hypocalcemic ventricular depression.

A single study in patients with lactic acidosis treated with sodium bicarbonate failed to reveal any significant changes in venous lactate concentration, hemoglobin affinity for oxygen, total body oxygen consumption, oxygen extraction ratio, transcutaneous oxygen pressure, serum sodium concentration, or osmolality.[56] However, the dose of bicarbonate (1 mmol/kg) was small. Another study of three patients treated with sodium bicarbonate (mean dose, 90 mEq) during cardiac arrest revealed a rise in osmolality from 308 to 343 mosm/kg.[58]

In summary, many potentially detrimental effects of bicarbonate administration have been identified, but their clinical relevance has not been established.

Other Alkalinizing Therapies: Carbicarb, Dichloroacetate, Tris-Hydroxymethyl Aminomethane, and Dialysis

Carbicarb is an equimolar mixture of sodium carbonate and sodium bicarbonate. Compared with sodium bicarbonate, Carbicarb raises the SID (thereby the pH) far more[45,48,49,54,62] and boosts the PCO_2 far less[48,49,64] when given IV to animals with

metabolic acidosis. To the extent that the failure of sodium bicarbonate to effect hemodynamic improvement is caused by the generation of carbon dioxide, Carbicarb might be superior. Carbicarb more consistently increases intracellular pH,[49,62,64] and although it improved hemodynamics in two studies,[11,49] it did not in three others.[48,62,64]

DCA is a compound that probably works by stimulating the pyruvate dehydrogenase complex, the rate-limiting enzyme that regulates the entry of pyruvate into the tricarboxylic acid cycle, thus promoting the clearance of accumulated lactate. In addition, DCA increases myocardial glucose utilization and contractility.[87] Although several animal and clinical trials showed that DCA could raise pH and bicarbonate concentration while lowering lactate concentrations, with little apparent toxicity,[52,88,89] a large, multicenter, placebo-controlled trial in patients with lactic acidosis failed to confirm improved hemodynamics or outcome.[3] This drug is not available commercially. Tris-hydroxymethyl aminomethane is a weak alkali that penetrates cells easily. Its potential to raise blood and intracellular pH without producing carbon dioxide has been confirmed in animal models of metabolic acidosis. Tris-hydroxymethyl aminomethane also improved myocardial contraction and relaxation in an isolated rabbit heart preparation.[71] Although tris-hydroxymethyl aminomethane is commercially available, complications of hyperkalemia, hypoglycemia, extravasation-related necrosis, and neonatal hepatic necrosis are likely to limit its use.

There have been many case studies that report the use of dialysis to control the volume and sodium loads that accompany sodium bicarbonate infusion. In most of these reports, sodium bicarbonate alone did not improve the pH or lactate concentrations, but bicarbonate-buffered peritoneal dialysis did. Perhaps importantly, peritoneal dialysis was very effective at removing lactate. The returned dialysate contained between 2.6 mEq/L and 14 mEq/L of lactate in one study,[90] and the calculated lactate clearance by peritoneal dialysis averaged 21 mL/min in another.[91] The impact of bicarbonate infusion plus dialysis on cardiovascular function and outcome has not been studied systematically, nor has the relevance of the bicarbonate component of this potential treatment been examined.

Conclusion

Sodium bicarbonate is clearly effective in raising the arterial pH in critically ill patients with lactic acidosis. The impact on intracellular pH is unknown in such patients, but extrapolation from extensive animal studies suggests that it is negative. Despite the correction of arterial acidemia, sodium bicarbonate, like DCA, has no favorable cardiovascular effects, even for patients with severe acidemia and receiving continuous infusions of catecholamines. Although hemodynamic improvement is not the only mechanism by which bicarbonate might be beneficial, animal studies have failed to yield alternatives. Even theoretical arguments in favor of sodium bicarbonate administration rely on a naïve representation of acid-base physiology, ignoring the complex compartmentalization of pH, the second-level effects of bicarbonate infusion, the impact of carbon dioxide generation, or the negative consequences of hyperlactatemia. We believe most clinicians who continue to use bicarbonate for patients with severe lactic acidosis do so largely because of their inclination to action: How can I "fail" to give bicarbonate when no alternative therapy is available and the mortality of this condition is so high?

The oft-cited rationale for bicarbonate use, that it might ameliorate the hemodynamic depression of metabolic acidemia, has been disproved convincingly. Any future role for bicarbonate in these patients depends on the formulation of new hypotheses of efficacy followed by animal and clinical studies to seek to confirm any proposed benefit. Given the current lack of evidence supporting its use, we cannot condone bicarbonate administration for patients with lactic acidosis. We extend this to those with $pH < 7.2$ on vasoactive drugs, inasmuch as bicarbonate has no measurable beneficial effects even in these sickest patients. Indeed, we do not give or advise bicarbonate infusion regardless of the pH.

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Development of an oral formulation of omeprazole

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Pilbrant Å, Cederberg C. Development of an oral formulation of omeprazole. Scand J Gastroenterol 1985;20(suppl 108):113-120.

Omeprazole has a low water solubility and is chemically labile in an acid environment. In the formulation of an oral dosage form of omeprazole the possibilities of dissolution rate limited absorption and preabsorption degradation must be kept in mind. A water suspension of omeprazole was tested in a pilot bioavailability study. The suspension was given to six healthy, fasting volunteers on two occasions – together with sodium bicarbonate solution and together with the same volume of water. When the suspension was given with water the bioavailability was reduced by about 50 % owing to preabsorption degradation. In another bioavailability study the slowest of three granule formulations with differing *in vitro* dissolution rates showed a reduced extent of absorption.

A controlled-release pellet formulation (enteric-coated) was formulated and tested in a series of bioavailability studies. A single dose given with food resulted in a delayed absorption and possibly lower bioavailability than under fasting conditions. When the granules were given on an empty stomach before the morning meal the length of time between dosage and meal was of no importance. Concomitant administration of a liquid antacid had no influence on the bioavailability of omeprazole.

Key-words: Bioavailability; controlled release; dosage form; enteric coating; omeprazole; stability

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Introduction

Omeprazole (Figure 1) is a substituted benzimidazole which selectively inhibits the proton pump in the gastric mucosa (1, 2). Omeprazole is very slightly soluble in water, but is very soluble in alkaline solutions as the negatively charged ion. It is an ampholyte with $pK_a \sim 4$ (pyridinium) and 8.8 (benzimidazole).

Omeprazole degrades very rapidly in water solutions at low pH-values. Figure 2 shows a plot of the logarithm of the observed rate constants for degradation as a function of pH. In each experiment, the initial, pseudo-first-order rate of degradation was calculated from the amount of unchanged omeprazole in buffer solutions (3). The rate of degradation proceeds with a half-life of less than 10 minutes at pH-values below 4. At pH 6.5 the half-life of degradation is 18 hours; at pH 11 about 300 days.

Preformulation studies have shown that moisture, solvents and acidic substances have a deleterious effect on the stability of omeprazole and should be avoided in pharmaceutical formulations.

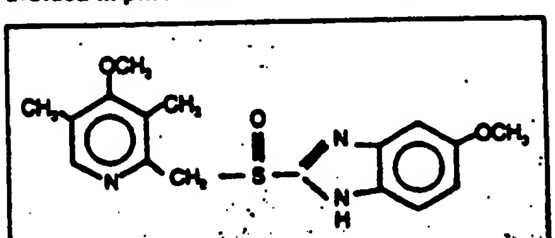

Figure 1. Omeprazole. H 168/68. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole.

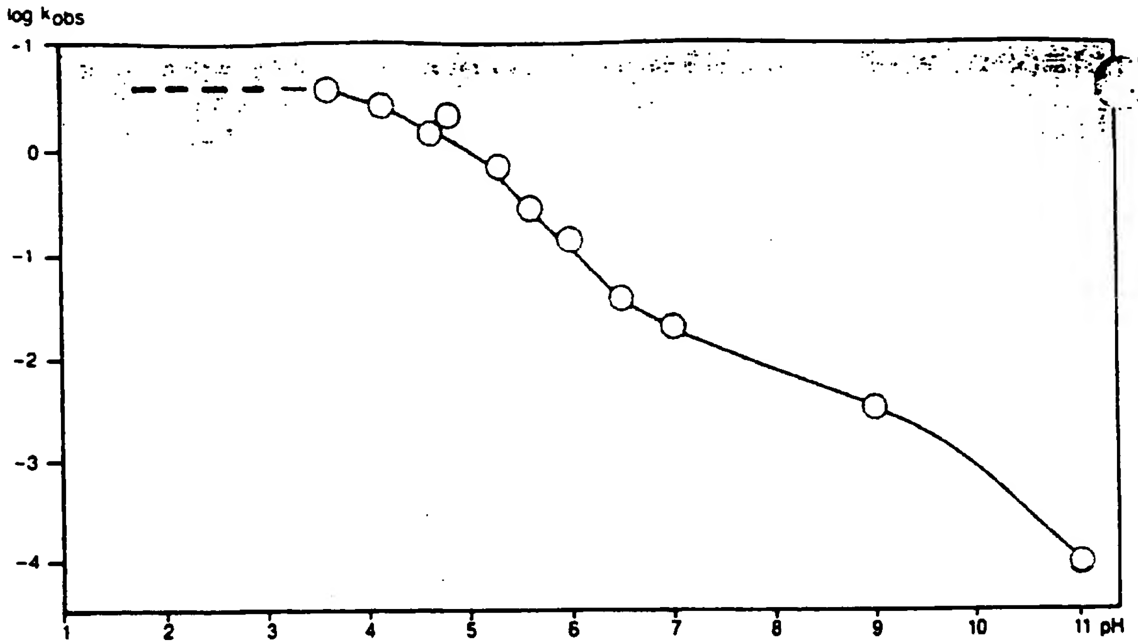

Figure 2. Logarithm of the observed rate constant (k_{obs}, h^{-1}) for the initial, pseudo-first-order degradation of omeprazole in water solution at constant pH, plotted as a function of pH.

The aim was to develop a stable, oral, pharmaceutical formulation of omeprazole in doses of 20–60 mg, with acceptable bioavailability characteristics.

Pharmaceutical considerations

For a substance which is very slightly soluble in water and which rapidly degrades in the acid environment of the stomach, there is a limited number of options as far as pharmaceutical development is concerned.

Solutions

In animal experiments and in initial studies in man it is highly preferable to use water solutions of the drug in order to avoid influences of the dosage form on the pharmacokinetics and pharmacodynamics of the drug. Omeprazole is, however, only soluble in alkaline water solutions with physiologically unacceptable, high pH-values.

Suspensions

In toxicological and phase I clinical studies, suspensions of omeprazole in water were used. Micronised omeprazole - particle surface area larger than 2.5 m^2/g – was suspended in a 0.25 % water solutio[n] of methylcellulose also containing sodium bicarbonate as pH buffer. The suspensions can be stored at refrigerator temperature for a week, or stored deep frozen for more than a year, and still retain 99 % of their initial potency. To avoid acidic degradation of omeprazole, the suspensions must be administered orally together with large amounts of pH buffering substances.

Solid dosage forms

There are two principle options for the formulation of an oral, solid dosage form of omeprazole:

- A conventional oral dosage form from which omeprazole is released and absorbed rapidly enough to avoid degradation in the stomach.
- An enteric-coated dosage form, which releases omeprazole for absorption in the small intestine.

The first option was ruled out in a pilot bioavailability study (see below), where it w[as] shown that more than half of the omeprazole in rapidly dissolving dosage form degrades in the stomach.

p 114 + 116 . Pilbrant + Cederberg

An enteric-coated dosage form, which does not release the active ingredient for dissolution and absorption until it has been transported down to the neutral reacting part of the small intestine, offers the best possibilities. The dosage form – a tablet, a capsule or granules – is coated with a polymer, which is insoluble in acid media but soluble in neutral to alkaline media. Depending on the choice of polymer and on the thickness of the coated layer, the pH-solubility profile of the enteric-coating can be controlled.

An enteric-coated dosage form of omeprazole must be perfectly coated and acid resistant, since, if any drug leaks out of the dosage form in the stomach, it is almost immediately degraded. The same is the case if an acidic medium can diffuse into the dosage form through pin-holes or damage in the enteric-coating.

Solid particles of a size exceeding 2–4 mm, such as enteric-coated tablets or capsules, are known to remain in the stomach for a long time before they are emptied into the small intestine (4–6). Non-disintegrating, coated tablets administered together with food were found to stay in the stomach for more than 14 hours (7). Enteric-coated aspirin tablets showed a prolonged and erratic gastric emptying, while enteric-coated granules of a size of about 1 mm dispensed in hard gelatine capsules dispersed in the content of the stomach and gradually emptied in to the small intestine in a reproducible way (5).

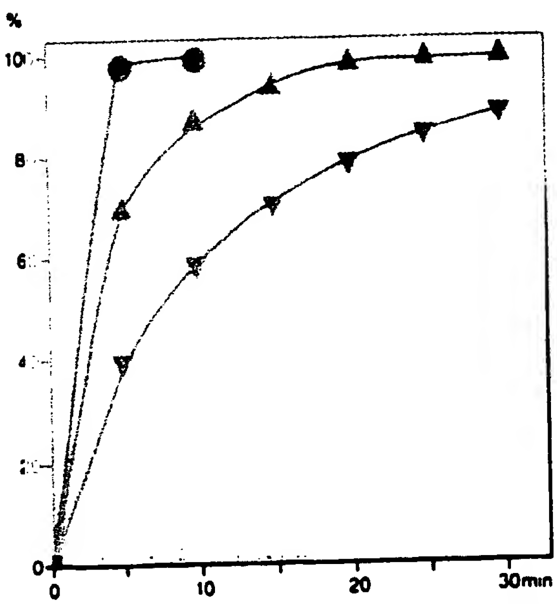

Figure 3. Dissolution of omeprazole from three granule formulations *in vitro* in phosphate buffer, pH = 6.5. The cumulative amount dissolved (%) is plotted as a function of time.

● granules, batch H 370-9-1
▲ granules, batch H 370-8-1
▼ granules, batch H 370-1-1

In the pharmaceutical manufacture of coated dosage forms, it is impossible to coat every single unit in a batch perfectly. A small fraction of units will have imperfect coating, or else be damaged during further handling and transport. For a single unit, enteric-coated dosage form of omeprazole, e.g. a tablet, there is always a small risk that all omeprazole contained in the dose can be degraded in the stomach. For a multiple unit, enteric-coated dosage form, e.g. enteric-coated granules dispensed in a hard gelatine capsule, only the omeprazole contained in a few pellets out of a total of hundreds is lost. Our efforts were, therefore, concentrated on developing an enteric-coated granule formulation.

Formulation and *in vitro* testing

In the formulation of a solid dosage form of omeprazole, having a low water solubility of 0.1 mg/ml, there is always the risk of dissolution rate limited absorption. Three spherical granule formulations containing 10 % of omeprazole were manufactured and classified. The fraction with a diameter between 0.7 - 1.0 mm was used for further studies.

The dissolution rate *in vitro* was determined using a slightly modified beaker method according to Levy and Hayes (8). 500 ml of deaerated phosphate buffer pH 6.5, ionic strength 0.1, was kept at +37 °C and stirred at a rate of 100 rpm. An amount of granules corresponding to 10 mg of omeprazole was added and the amount dissolved determined from the continuous recording of the absorbance at 300 nm in a spectrophotometer using 1 cm flow cells. The cumulative amount dissolved is plotted as a function of time in Figure 3. All three formulations released most of their content of omeprazole within 30 minutes.

A pilot bioavailability study showed that the two faster dissolving granules were absorbed to the same extent, while the extent of absorption of the more slowly dissolving granules was reduced.

Rapidly dissolving, spherical granules containing 10 % of omeprazole were enteric-coated with approximately 15 % by weight of polymer. The coating was sprayed onto the granules from an organic solvent solution in a fluidised bed apparatus. After drying, the coated granules were analysed and dispensed in hard gelatine capsules.

The granules were tested for acid resistance *in vitro* in the following way: An amount of granules corresponding to 10 mg of omeprazole was dispersed in 500 ml of 0.1 molar hydrochloric acid at a temperature of +37 °C. Stirring was done with a paddle at a rate of 100 rpm. After two hours the granules were removed from the vessel, rinsed with water, dried and analysed for omeprazole by liquid chromatography. After two hours exposure to acid more than 85 % of the initial amount of omeprazole was recovered. When tested for dissolution rate *in vitro* in a medium of pH 6.5, more than 90 % dissolved within 15 minutes.

Omeprazole capsules have an acceptable storage stability when stored in a proper package. The stability characteristics of omeprazole – the substance is sensitive to moisture – necessitate the presence of a desiccant in the package.

Bioavailability evaluation of dosage forms

Omeprazole suspension given with and without pH-buffers

The solubility and stability properties of omeprazole prevent the use of water solutions as the reference formulation in animal and human studies. A rapidly dissolving suspension of micronised omeprazole is the second best choice as the reference formulation. However, since omeprazole degrades rapidly in an acid environment, it is essential to know the magnitude of the degradation occurring prior to the absorption of an oral dose. A pilot bioavailability study was therefore performed using six healthy, male volunteers.

A suspension of micronised omeprazole, 60 mg, in water, 50 ml, also containing 8 mmoles of sodium bicarbonate (pH = 9) was administered in the following way: In the morning, after fasting for at least ten hours, the volunteers were given a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later the volunteers took the omeprazole suspension and rinsed it down with another 50 ml of sodium bicarbonate solution. 10, 20, and 30 minutes later, a further 50 ml of sodium bicarbonate solution was taken. The amount of sodium bicarbonate is sufficient to buffer the pH of the gastric content to neutral values for at least 45 minutes.

In another experiment, a suspension of omeprazole in water (pH adjusted to 9 by sodium hydroxide) was administered according to the same protocol as above but with the sodium bicarbonate solutions replaced by water. Doses were given in random order with a week's interval between doses. Venous blood was sampled frequently over a period of four hours and blood plasma was analysed for omeprazole by liquid chromatography (9).

The results of the plasma analyses are shown in Figure 4. The absorption of omeprazole proceeds rapidly and peak plasma concentrations were

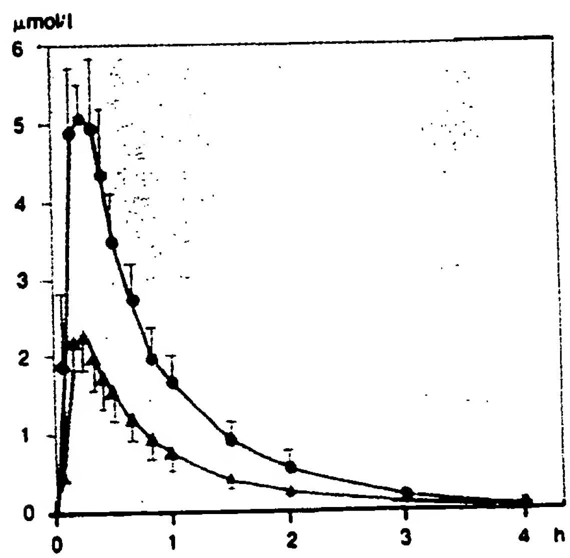

Figure 4. Plasma concentration of omeprazole in [illegible] healthy, fasting volunteers, mean + or – SEM after o[illegible] administration of omeprazole, 60 mg, given as:
● buffered suspension
▲ suspension without buffer

reached after a mean of 13 minutes in both experiments. The area under the plasma concentration time curve (AUC) was calculated by the trapezoidal method up to four hours after administration and extrapolated to infinity by dividing the last plasma concentration by the negative slope of the terminal, linear part of the log/linear plasma concentration time curve.

When the omeprazole suspension was given together with sodium bicarbonate buffer, the mean AUC was 4.8 µmol x h/l (range 2.8 – 8.8). Without the buffer protection the AUC was reduced to a mean of 2.1 µmol x h/l (44 %), indicating that more than half of the dose was lost due to degradation in the acidic stomach.

A straight-forward pharmacokinetic analysis of the data showed that the absorption of omeprazole was rapid and completed within the period during which the stomach was neutral. The results clearly show that a conventional, non-buffered, oral dosage form of omeprazole will have a low systemic bioavailability owing to preabsorption degradation of omeprazole in the stomach.

Bioavailability of granules – influence of dissolution rate

A pilot bioavailability study in six, healthy volunteers was performed in order to clarify the influence of the dissolution rate on the absorption of omeprazole. Three granule formulations – the dissolution curves are shown in Figure 3 – were tested using buffered suspension as the reference formulation. In order to avoid problems with the degradation of omeprazole, doses of 60 mg were given together with sodium bicarbonate, as described above. Venous blood was frequently sampled and blood plasma analysed for omeprazole (9). The AUC for the two faster dissolving granules (H 370-9-1 and H 370-8-1) relative to that of the reference formulation was 95 and 92 %, respectively. The granules with the lowest *in vitro* dissolution rate (H 370-1-1) were absorbed to a lower extent and had a mean relative AUC of 73 % only. The mean peak plasma concentration for granules H 370-1-1 was reached about 20 minutes later than for the other two granule formulations and for the suspension, also indicating a lower rate of absorption.

From this experiment, it can be concluded that the *in vitro* dissolution rate method used can discriminate between acceptable and non-acceptable batches. In order to be fully absorbed, the *in vitro* dissolution rate should be as high as, or higher than, that of granules H 370-8-1.

Bioavailability of enteric-coated granules

Six, healthy, male volunteers participated in a three-way, cross-over bioavailability study. They received, in random order, 60 mg single, oral doses of omeprazole either as a buffered suspension given together with sodium bicarbonate solution, or as enteric-coated granules dispensed in hard gelatine capsules given together with 300 ml of water on an empty stomach or as enteric-coated granules in capsules together with a meal. In each experiment, standardised meals were served 2.5 and 6 hours after administration of the dose. Venous blood was sampled frequently for four hours (suspension) or seven hours (granules). Blood plasma was analysed for omeprazole by liquid chromatography according to Persson et al (9).

The results of the plasma analyses are shown in Figure 5. The absorption of omeprazole after the suspension was given was rapid, and peak plasma concentrations were reached within 10 – 20 minutes. After administration of the enteric-coated

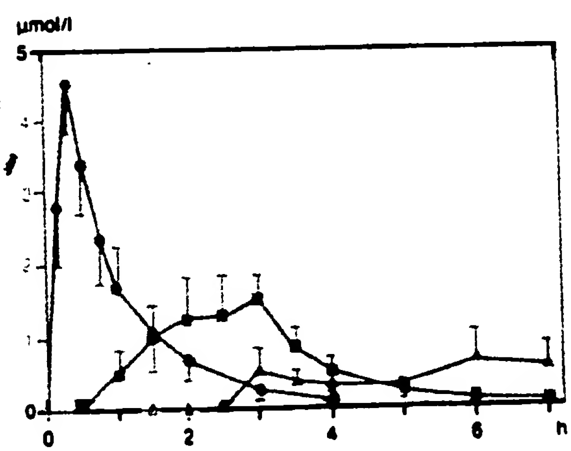

Figure 5. Plasma concentration of omeprazole, mean + or - SEM, in six healthy volunteers given 60 mg single oral doses of omeprazole as:
● buffered suspension
■ enteric-coated granules before breakfast
▲ enteric-coated granules with breakfast

granules a certain time was required for gastric emptying and for dissolution of the enteric-coating before absorption of omeprazole started. In most cases, gastric emptying occurred in connection with the meal served 2.5 hours after the dose. In one subject, when enteric-coated granules were given with food, gastric emptying of granules did not start until in connection with the second meal, served six hours after the dose.

The plasma concentration-time curves obtained after administration of enteric-coated granules were flat and broad, and peak plasma concentrations were low. The total amount absorbed, as reflected by the AUC, was, however, only decreased by 14 % when the granules were given on an empty stomach in comparison with the buffered suspension. The corresponding figure for enteric-coated granules administered with a meal is higher, but since absorption of omeprazole was not completed in all subjects when the experiment was terminated, the exact figure is unknown. Although this study is not fully conclusive regarding the bioavailability of omeprazole given with food, it is recommended that omeprazole should be taken in the morning before breakfast.

The effect of omeprazole on gastric acid secretion is long lasting (10). The effect is not a direct function of blood concentration of omeprazole at any time, but is rather a function of the total amount of omeprazole reaching the general circulation, i.e., directly proportional to the AUC (2, 10). This means that the same pharmacological effect is achieved with dosage forms of omeprazole producing equal AUCs. The shapes of the plasma concentration-time curves are of no importance.

Bioavailability of enteric-coated granules administered at different times before breakfast

When omeprazole enteric-coated granules are given with a meal, the rate of absorption of omeprazole is reduced. Patients are therefore recommended to take the dose on an empty stomach before the morning meal. However, in clinical practice it is necessary to know what length of time is required between dosing and food intake. To be able to answer the question, we performed a bioavailability study comparing omeprazole enteric-coated granules given 15 minutes before the breakfast with the same dose given 2 minutes before the meal. A buffered suspension was again used as the reference formulation. Twelve healthy volunteers participated in the study. The doses were given as described above. Standardised meals were served after 2.5, 6, 10 and 13 hours. Blood samples were collected over a period of 6 hours (suspension) and 24 hours (granules).

Eleven of the subjects completed the study and are included in the results. The resulting mean plasma concentration time curves are shown in Figures 6 and 7. It is interesting to note that the absorption of omeprazole from the enteric-coated granules in some subjects started as early as 30 minutes after the dose and that most subjects had a second plasma concentration peak shortly after the second meal served 2.5 hours after dose.

The AUC, relative to that of the reference formulation, was very similar in the two experiments wit

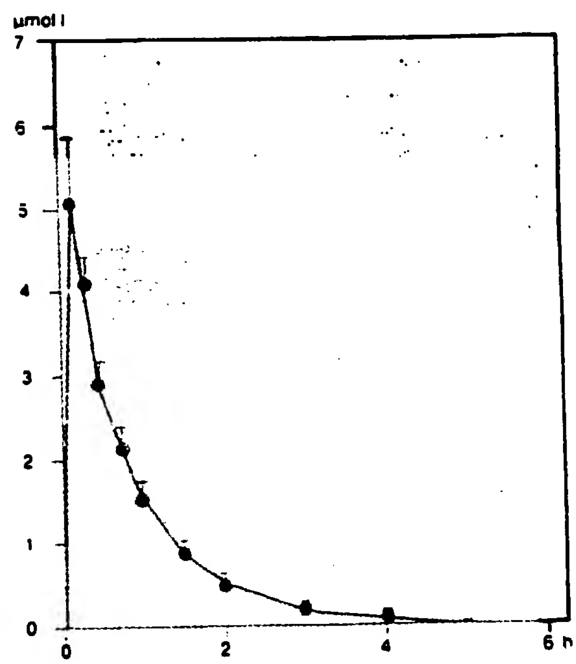

Figure 6. Plasma concentration of omeprazole, mea + or − SEM, in eleven healthy volunteers given a 60 mg single, oral dose of omeprazole as a buffered suspension under fasting conditions.

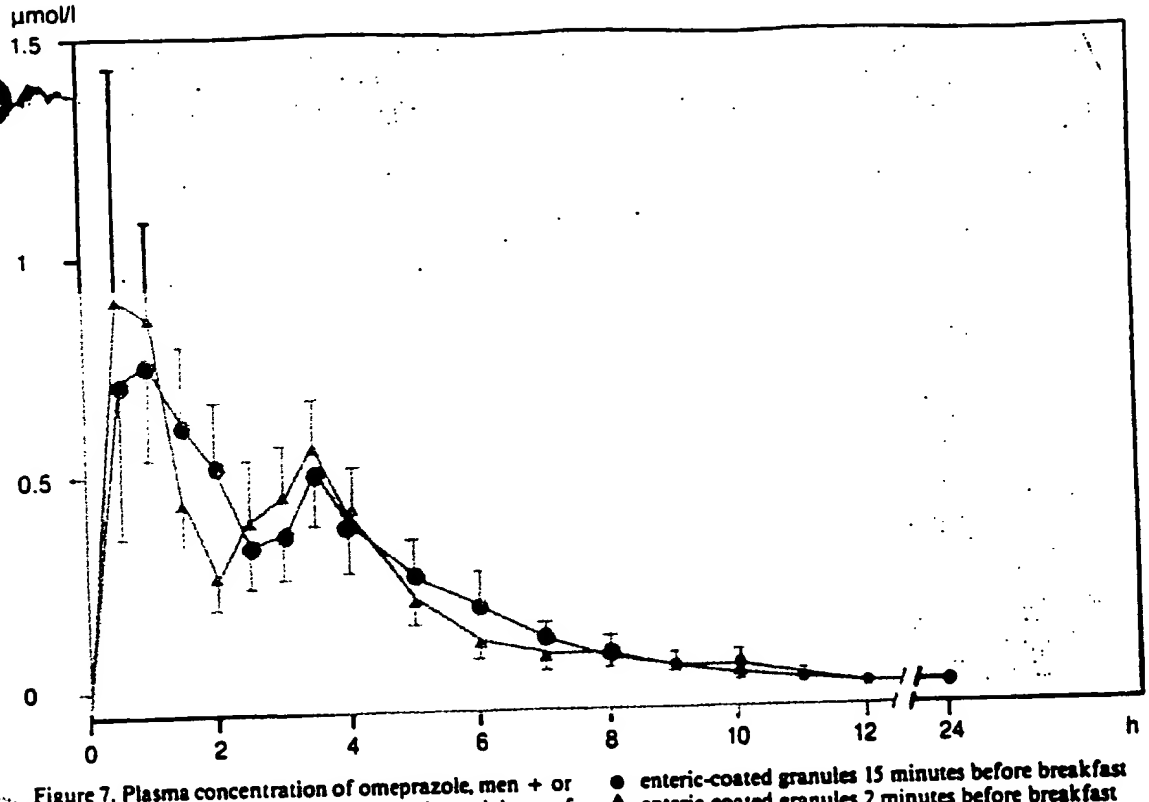

Figure 7. Plasma concentration of omeprazole, men + or - SEM, in eleven healthy given 60 mg single, oral doses of omeprazole as:

enteric-coated granules; 65.5 % when given 15 minutes before breakfast and 66.6 % when given 2 minutes before breakfast. The variability in the AUC between doses within subjects was small, as can be seen in Figure 8. The conclusion of this study is that the omeprazole dose can be given before the morning meal, and that there is no need to specify any time between the administration and the start of the morning meal.

Bioavailability of enteric-coated granules - interaction with antacids

In the clinical treatment of ulcer, antacids are often prescribed together with inhibitors of gastric acid secretion. Antacids may interfere with the function of an enteric-coated dosage form and cause dissolution of the coating in the stomach. For omeprazole this could mean an increased risk of degradation in the stomach. We therefore tested the influence of a liquid antacid on the bioavailability of omeprazole enteric-coated granules.

Six healthy volunteers were given, in random order, enteric-coated granules with and without concomitant administration of an aluminium-magnesium hydroxide/carbonate suspension. The dose was given on an empty stomach and venous blood samples collected during a period of seven hours. In one experiment the subjects were pretreated with antacid the day before the omeprazole administration. 10 ml doses of a liquid antacid with an acid-binding capacity of 85 mmol per dose (Novaluzid®, AB Hässle, Sweden) were given one and three hours after each meal and at bed time; a total of seven doses. On the morning of the next day, another 10 ml dose was given just prior to the dose of omeprazole enteric-coated granules. In the other experiment omeprazole enteric-coated granules were administered without antacid treatment.

The results of the plasma analyses are summarised in Figure 9, which shows the individual and mean AUCs. The mean AUC was practically identical in the two experiments. As can be seen in Figure 9, the variability in the AUC within each subject is small,

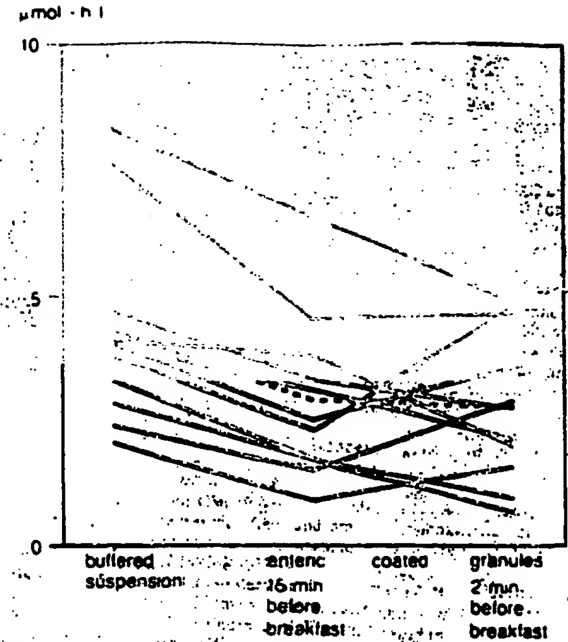

Figure 8. AUC (μmol × h/l) in eleven healthy volunteers given 60 mg single, oral doses of omeprazole as a buffered suspension and enteric-coated granules 15 or 2 minutes before breakfast.
——— individual values
- - - - - mean values

whereas the variability between subjects is substantial.

Conclusion: Co-administration of antacids has no influence on the bioavailability of omeprazole given as enteric-coated granules.

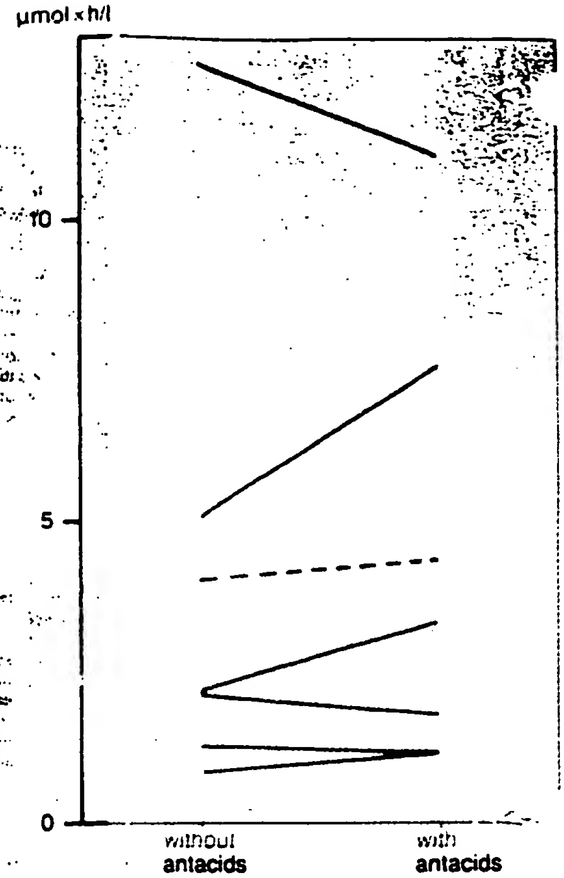

Figure 9. AUC (μmol × h/l) in six healthy volunteers given 60 mg single, oral doses of omeprazole enteric-coated granules with and without antacids.
——— individual values
- - - - - mean values

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Duodenal Intracellular Bicarbonate and the 'CF Paradox'

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Summary

HCO_3^- secretion, which is believed to neutralize acid within the mucus gel, is the most studied duodenal defense mechanism. In general, HCO_3^- secretion rate and mucosal injury susceptibility correlate closely. Recent studies suggest that luminal acid can lower intracellular pH (pH_i) of duodenal epithelial cells and that HCO_3^- secretion is unchanged during acid stress. Furthermore, peptic ulcers are rare in cystic fibrosis (CF), although, with impaired HCO_3^- secretion, increased ulcer prevalence is predicted, giving rise to the 'CF Paradox'. We thus tested the hypothesis that duodenal epithelial cell protection occurs as the result of pH_i regulation rather than by neutralization of acid by HCO_3^- in the pre-epithelial mucus. Cellular acidification during luminal acid perfusion, and unchanged HCO_3^- secretion during acid stress are inconsistent with pre-epithelial acid neutralization by secreted HCO_3^-. Furthermore, inhibition of HCO_3^- secretion by 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB) despite preservation of pH_i and protection from acid-induced injury further question the pre-epithelial acid neutralization hypothesis. This decoupling of HCO_3^- secretion and injury susceptibility by NPPB (and possibly by CF) further suggest that cellular buffering, rather than HCO_3^- exit into the mucus, is of primary importance for duodenal mucosal protection, and may account for the lack of peptic ulceration in CF patients.

The location of the duodenum just distal to the gastric antrum and proximal to the pancreaticobiliary ducts uniquely exposes its leaky epithelium to a low pH environment due to peristaltically conveyed pulses of concentrated gastric acid, which vary luminal pH between two and seven on a scale of minutes [1, 2, 3]. Rapid shifts of duodenal pH are likely to create intense stress on the epithelial cells to maintain constant intracellular pH (pH_i) in order to maintain function and prevent irreversible necrosis due to intracellular acidification [4, 5]. The currently held explanation as to why the cells are protected is that active epithelial bicarbonate secretion forms a neutralizing barrier in the pre-epithelial mucus, preventing acid penetration into the cells [6].

Cystic fibrosis (CF) is an inherited disease caused by mutations of the cystic fibrosis transmembrane regulator or cystic fibrosis transmembrane conductance regulator (CFTR). Impaired duodenal and pancreatic HCO_3^- secretion characterizes patients afflicted with this disease, which, combined with normal or supernormal gastric acid secretion, produces abnormally high acidity in the upper gastrointestinal tract. Consequences of this

acidity are erosive esophageal disease, pulmonary acid reflux, and inactivation of secreted pancreatic enzymes. Despite these marked acid-related àbnormalities, these patients are remarkably resistant to peptic duodenal ulceration, a phenomenon yet unexplained. In this report, we will propose and we will experimentally test what we will term the 'CF Paradox' in an attempt to explain this apparent protection from duodenal injury.

Bicarbonate has been thought to be the major means by which the duodenal epithelium was protected from acid-induced injury. It is a logical duodenal defense mechanism for the following reasons: 1) Duodenal bicarbonate secretion/cm^2 epithelium much greater than gastric bicarbonate secretion [7, 8, 9, 10]; 2) pH electrode studies suggest that epithelial bicarbonate secretion creates a layer of neutral pH next to the mucosa [11, 12, 13]; 3) *Helicobacter pylori* infection complicated by duodenal ulcers is associated with diminished bicarbonate secretion, and eradication of *Helicobacter pylori* infection restores duodenal bicarbonate secretory capacity [14, 15]. Furthermore, a strong correlation between bicarbonate secretion and mucosal injury susceptibility has been found in experimental animal models [16, 17, 18]. The mechanism by which bicarbonate is secreted from the epithelial cell is controversial. Bicarbonate is transported from the blood across the epithelial cell basolateral membrane by a variant of the sodium-bicarbonate transporter (NBC), in response to decreased pH_i resulting from exposure to luminal acid. Alternatively, bicarbonate can be formed in the epithelial cell cytoplasm from condensation of gaseous in-diffusing CO_2 and water catalyzed by carbonic anhydrase, with generated protons exiting via a basolateral Na^+/H^+ exchanger 1 (NHE1) [19, 20]. Since inhibiting or eliminating the apical membrane CFTR greatly attenuates bicarbonate secretion [21, 22], the CFTR has been implicated in the mechanism of bicarbonate secretion, although it is unknown whether it serves directly as a bicarbonate channel, or indirectly to preserve transmembrane electrical or ion gradients.

We have re-examined the role of bicarbonate secretion in overall duodenal defense from acid, and, in doing so, have formulated a novel hypothesis with regard to the role of bicarbonate transport. To test these possibilities, we developed a technique for the measurement of pH_i in the duodenum of anesthetized rats [23]. With this system, we could perfuse solutions of varying pH through a chamber placed over the exposed duodenal mucosa, thereby simulating changes in luminal pH. With this system, we exposed the mucosa to a brief pulse of acid, which promptly decreased pH_i. This fall of pH_i, even with mildly acidic perfusates, suggested that acid could readily penetrate the overlying mucus gel and the mucosa, therefore calling into question the role of pre-epithelial bicarbonate neutralization in duodenal mucosal defense. With removal of the acid challenge, pH_i was elevated to supernormal values, which indicated that cellular buffering power has increased, not decreased, during acid challenge. Furthermore, a second acid challenge acidified pH_i less than the first; further confirming that acid exposure was associated with increased cellular buffering power. This somewhat surprising finding was confirmed by comparison with prior studies conducted in a variety of systems, in which acid pulses were followed by pH_i overshoot, indicative of increased buffering power in cells containing a plasma membrane base-loading mechanism such as sodium-bicarbonate cotransport [24].

Further studies indicated that this buffering power increase was inhibited by the stilbene anion transport inhibitor 4,4'diisothiocyanostilbene-2,2'-disulfonic acid (DIDS). When exposed to two short acid pulses, pH_i decreased less during the second challenge; again strongly suggestive that cellular buffering power was increased during acid exposure. DIDS inhibited this adaptive

effect. Our studies were thus consistent with bicarbonate uptake being induced by luminal acid exposure by a DIDS-inhibitable mechanism, which is most likely a sodium-bicarbonate cotransporter (NBC), presumably located on the basolateral, blood-facing cellular pole. This finding was expected insofar as primary isolated duodenal epithelial cells recovered from acid exposure by a mechanism consistent with the activity of an NBC [25], and that bicarbonate-secreting pancreatic duct cells have a basolateral membrane NBC [26]. A recent study confirms the presence of a NBC1 in the basolateral membrane duodenal epithelial cells [27].

Base loading during acid challenge, which increases cellular buffering power and attenuates the fall of pH_i, is an attractive means of defending the epithelium from acid challenge. To address how bicarbonate secretion is related to this observation, we performed parallel experiments in which bicarbonate secretion was measured in a perfused duodenal loop exposed to the same pH perfusion sequence as the measurements of pH_i. We found that titratable alkalinity increased substantially during acid perfusion, although, total CO_2 content decreased somewhat at the same time. The best explanation for these data was that although acid back-diffusion increased markedly during luminal acid perfusion, bicarbonate secretion was unchanged, inconsistent with its putative protective function. The implications of these data, combined with our measurements of pH_i, support our hypothesis that increased cellular buffering, and not bicarbonate secretion, is the primary duodenal defense mechanism from acid. Acid was not neutralized at the duodenal surface, since cellular pH_i clearly decreased during acid challenge, and since acid back-diffusion was the major means of acid loss when perfused over the mucosa. Furthermore, since bicarbonate secretion was unchanged during acid perfusion, and only increased after acid removal, bicarbonate cannot be a major

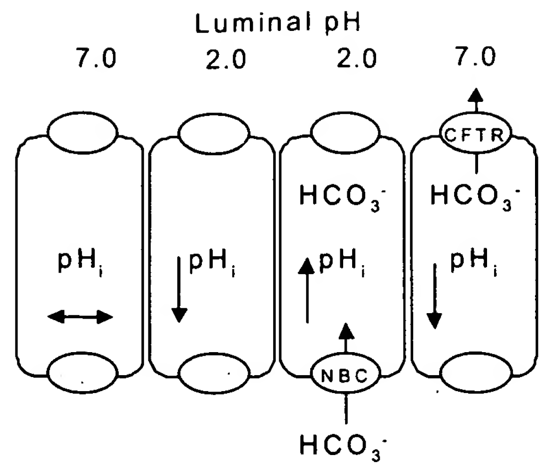

Figure 1. Sequential response of duodenal epithelial cells to luminal acid. In the left panel, steady-state pH_i about 7.1 when no acid is present. In the succeeding panels to the right, luminal acid rapidly acidifies the epithelial cells. Low pH_i increases the activity of the basolateral sodium-bicarbonate cotransporter (NBC), which increases cellular bicarbonate concentration, increasing cellular buffering power. When luminal pH returns to neutrality, acid diffuses out of the cell. The excess intracellular base produces a supernormal pH or overshoot. This in turn activates the bicarbonate secretory mechanism (CFTR), which produces bicarbonate secretion.

protective mechanism, since its increased secretion is present only when it is not needed i.e. when acid is no longer present. In this proposed mechanism, shown in Figure 1, bicarbonate secretion occurs to remove excess alkali from the cell when excess intracellular bicarbonate is no longer needed after acid challenge.

In our most recent studies, we have used the inhibitors DIDS and NPPB in order to further test our hypothesis. Both inhibitors abolished bicarbonate secretion, as has been published previously [28, 29]. DIDS decreased pH_i of the duodenal cells whereas NPPB increased pH_i. These effects on pH_i were consistent with inhibition of base uptake and exit from the cell, respectively. We then showed that susceptibility of the epithelial cells to acid injury was enhanced by DIDS but decreased by

NPPB. We thus were able to uncouple bicarbonate secretion from mucosal protection, since NPPB inhibited bicarbonate secretion while enhancing injury susceptibility. These data added further evidence that intracellular pH regulation, and not secreted bicarbonate, appears to be of prime importance for duodenal mucosal protection.

We have formulated the 'CF Paradox', in which we pose the question: why is the prevalence of duodenal ulcers not increased in patients with CF? Patients with CF, for example, have high normal acid secretion [30], and must take gastric antisecretory medications in order to diminish esophageal acid reflux and to prevent acid-mediated inactivation of pancreatic enzymes [31, 32]. Furthermore, pancreatic and duodenal bicarbonate secretion are presumably impaired by the disease [22], and duodenal pH is lower than normal [33]. *Helicobacter pylori* infection prevalence resembles that of the unaffected population [34]. Combined with the frequent prevalence of chronic lung disease, these patients should be a high risk for peptic ulceration. Clinical experience, and the literature, however, does not support an increased incidence of peptic ulceration is this population, but rather, it appears that the prevalence of peptic ulceration may actually be diminished [35, 36].

We propose that the impairment of duodenal bicarbonate secretion in the disease may explain why this population may be protected from peptic ulceration. Recall that the CFTR is needed for duodenal bicarbonate secretion. If the cells can base load normally via a basolateral NBC, or CO_2 diffusion, but cannot secrete bicarbonate across the apical membrane due to defective CFTR functioning, 'bicarbonate trapping' may occur. Elevated intracellular bicarbonate concentrations would create a new set point in which cellular buffering was elevated compared with non-affected cells, protecting the cytoplasm from irreversible acidification during acid stress.

Key words Bicarbonates; Cystic Fibrosis; Fluorescence; Hydrochloric Acid; Hydrogen-Ion Concentration; Ion Channels; Ion Transport; Microscopy; Rats

Abbreviations CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; DIDS: 4,4'diisothiocyanostilbene-2,2'-disulfonic acid; NBC: sodium-bicarbonate cotransporter; NHE: Na^+/H^+ exchanger; NPPB: 5-nitro-2-(3-phenylpropylamino) benzoic acid; pH_i: intracellular pH

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CLINICAL THERAPEUTICS/VOL. 10, NO. 2, 1988

Evaluation of Antacid Tablets and Liquid in Fasting and Fed Men and Women

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ABSTRACT

In view of in vitro tests suggesting good performance of an experimental tablet formulation of an aluminum hydroxide-magnesium hydroxide antacid, a study was conducted to evaluate the efficacy in vivo. Twenty-three healthy men and women were enrolled in the study, which was carried out in two parts: fasting and postprandial. Eight of the volunteers failed to qualify because of repeated baseline pH >2.5. In the 15 participants who qualified, the intragastric pH was monitored for up to 240 minutes after the administration of one or two experimental tablets, 5 or 10 ml of a commercially available liquid antacid, or placebo. In the fasting subjects ($n = 10$), the antacids rapidly increased the mean pH. One antacid tablet and 5 ml of liquid antacid yielded similar results, with mean peak pH values of 5.2 and 4.8 and durations above pH 3.5 of 25 and 40 minutes, respectively. When the doses were doubled, 10 ml of liquid produced a peak pH of 6.7 and maintained the pH above 3.5 for 40 minutes, whereas two tablets produced a peak pH of 4.8 and maintained pH above 3.5 for 15 minutes. In the fed subjects ($n = 10$), neither antacid formulation at either dose significantly raised intragastric pH. Further studies are needed to establish the optimal time for postprandial administration of antacids.

INTRODUCTION

Despite the advent of H_2 antagonists for treatment of peptic ulcers, antacids are still useful for treating esophagitis and less well-defined causes of dyspepsia,[1] and these disorders probably are responsible for a substantial proportion of total antacid consumption. Antacids based on aluminum hydroxide are the only type of antacid with well-documented efficacy in the treatment of gastroduodenal ulcer.[2] Many of the aluminum hydroxide formulations also contain magnesium salts to counteract the constipating effect of the

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aluminum and to further improve acid-binding capacity.

A good antacid is one that reacts rapi with acid, buffers in the pH range of : 6, has high acid-neutralizing capac (ANC), and causes few or minimal s effects. In addition to reducing the av able hydrogen ion content of the gas juice, antacids can bind bile acids : can inactivate pepsin if the intragas pH is brought above 5.5.[3]

Various in vitro tests have been dev oped for the evaluation of antacid p formance. The measurement of to neutralizing capacity is one widely u test.[4] Other tests, such as the pH-: test,[5] monitor the reaction rate, and : others measure performance under c ditions that are intended to resemble in vivo environment.[6] Several investi tors[7-9] have claimed good correlati between in vitro test results and in v efficacy, although the in vitro tests can take into account variations in anta activity due to changes in gastric moti and secretions and to interactions antacids with the gastric mucosa.

The presence of food in the stom profoundly affects the performance antacids. Berchtold and coworkers[10] ported that in vitro tests overestimat vivo neutralizing capacity of antacid the postprandial state. It is current pr tice to administer antacids one and th hours after meals, at which time considerable proportion of the meal been emptied and the remaining foo insufficient for buffering, especially s gastric secretion of acid is increasec the meal.[10] At one hour, the contin presence of some food prevents prema emptying of antacid from the stom Therefore, the interval between a m and antacid administration is critic terms of both gastric emptying and

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A good antacid is one that reacts rapidly with acid, buffers in the pH range of 3 to 6, has high acid-neutralizing capacity (ANC), and causes few or minimal side effects. In addition to reducing the available hydrogen ion content of the gastric juice, antacids can bind bile acids and can inactivate pepsin if the intragastric pH is brought above 5.5.[3]

Various in vitro tests have been developed for the evaluation of antacid performance. The measurement of total neutralizing capacity is one widely used test.[4] Other tests, such as the pH-stat test,[5] monitor the reaction rate, and still others measure performance under conditions that are intended to resemble the in vivo environment.[6] Several investigators[7-9] have claimed good correlations between in vitro test results and in vivo efficacy, although the in vitro tests cannot take into account variations in antacid activity due to changes in gastric motility and secretions and to interactions of antacids with the gastric mucosa.

The presence of food in the stomach profoundly affects the performance of antacids. Berchtold and coworkers[10] reported that in vitro tests overestimate in vivo neutralizing capacity of antacids in the postprandial state. It is current practice to administer antacids one and three hours after meals, at which times a considerable proportion of the meal has been emptied and the remaining food is insufficient for buffering, especially since gastric secretion of acid is increased by the meal.[10] At one hour, the continued presence of some food prevents premature emptying of antacid from the stomach. Therefore, the interval between a meal and antacid administration is critical in terms of both gastric emptying and pH.

Liquid formulations of antacids used to be considered more effective than tablets because liquids have shown more rapid and pronounced effects.[11] However, improved tablet formulations have been developed that react faster and have greater ANC. Antacid tablets are more palatable and more convenient than liquids, important considerations to ensure therapeutic compliance.[12] In light of these considerations and promising results from in vitro and clinical studies, interest has been renewed in tablet formulations of antacids.[5]

A new aluminum hydroxide-magnesium tablet has been formulated that has performed well in in vitro tests. We compared the efficacy of the tablet in vivo with that of a commercially available liquid antacid by measuring intragastric pH in healthy adults in both the fasted state and the postprandial state.

METHODS AND MATERIALS

The study was conducted in healthy men and women. Potential participants were excluded if they were pregnant, had irregular menstrual cycles, or had a history of intestinal or pyloric obstruction, gastric surgery, gastrointestinal hemorrhage, or other organic disease, including a recent positive finding of occult blood in the stool. They also were excluded if they had an acute infection, were receiving long-term salicylate therapy or had ingested salicylates within 24 hours before the study, had ingested alcohol within 48 hours before the study, had smoked within 24 hours before the study, or had used an antacid within 48 hours before the study.

The protocol was approved by the Ethics Committee of the Department of

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Medicine, University of Alberta and University of Alberta Hospitals. Written informed consent was obtained from all subjects before procedures were initiated.

The antacids used in the study were (1) commercially available liquid antacid containing 600 mg of aluminum hydroxide and 300 mg of magnesium hydroxide per 5 ml* (ANC = 28.3 mEq) and (2) experimental antacid tablets containing 400 mg of aluminum hydroxide, 400 mg of magnesium hydroxide, and 30 mg of simethicone per tablet (ANC = 25.4 mEq). The experimental tablets, prepared by Parke-Davis Canada, Inc, differed from commercially available tablets in the reactivity and method of manufacture of the acid-neutralizing component.

Study Design and Procedures

The study was conducted in two parts: "fasted" and "fed." Each part had a randomized five-way crossover design, using placebo and either 5 or 10 ml of the liquid antacid or one or two antacid tablets. Each antacid or placebo was tested during a four-hour session with at least one day separating test sessions. Subjects fasted from 10 PM of the previous evening. In the fasting phase of the study, food was not allowed for the duration of the test session.

A nose and throat examination was conducted before the study. Body temperature, blood pressure, and heart rate were recorded at the beginning and at the end of each test session.

On the morning of each test session, a nasogastric tube was positioned in the antrum of the stomach and secured in place. Subjects remained seated during the test. Gastric fluid (3 ml) was aspirated through the gastric tube by syringe, and pH measurements were made within one minute of withdrawal. The remainder of the sample was returned to the stomach with enough air to clear the tube.

Three baseline pH measurements were made before antacid administration to ensure the stability of the gastric pH. For a participant to qualify for the study, the pH of the aspirates had to be 2.5 or less on three consecutive samples and the variation between samples could be no more than 0.5. If these criteria were not met within 40 minutes, the subject was not allowed to participate on that day and was rescheduled for another day.

After oral administration of the antacid or placebo, the pH of gastric aspirate was measured in samples collected at the following times: 0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, 120, 150, 180, and 240 minutes.

In the second part of the study, the baseline pH measurements were obtained as in the first phase. A standard breakfast (glass of apple or orange juice, one scrambled egg, and a muffin or toast) was consumed over 15 minutes. The antacid or placebo was taken one hour after the start of the meal. Gastric aspirates were collected and pH measured at the following intervals from the baseline reading (immediately prior to start of meal): 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, and 240 minutes.

When a test session was completed, the nasogastric tube was removed. The participants were not allowed to eat or drink for 15 minutes and were kept under careful observation. No adverse reactions were reported by the volunteers or noted throughout the studies.

Data Analysis

Individual pH values at each time were used to calculate mean pH and standard deviations obtained for tablet or liquid antacid or placebo. Experimental antacid tablets (one or two tablets) and commercially available liquid antacid (5 and 10 ml) were compared with placebo and with each other using the following variables: peak pH, time to peak pH, and time above pH 3.5. Differences were analyzed by means of two-tailed *t* tests, with $P \leq 0.05$ considered statistically significant.

RESULTS

Twenty-three healthy volunteers were enrolled in the study, but eight failed to meet the baseline pH requirements so many times that they were permanently disqualified. Among the 15 qualifying participants, 21% of the baseline gastric pH values exceeded 2.5 (Table I). The nine men and six women who completed one or both parts of the study had a mean age of 24.9 ± 5.7 years and weighed

Table I. Baseline gastric samples fulfil

Participant Status	No. of Participants	Q
Qualified	15	
Disqualified	8	
Total	23	

* Baseline pH ≤2.5 with intersample variatio

*Trademark: Maalox® TC (Rorer Canada Inc, Bramalea, Ontario, Canada).

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Effect of Antacids in Fasting Subjects

The mean baseline pH was 1.79 in the placebo group, which was not significantly different from the baseline pH values in the antacid treatment groups (Table II). During the 240-minute period of study, intragastric pH values showed little change in the participants treated with placebo. However, after the ingestion of antacids, the pH of gastric fluid increased significantly as early as two minutes after administration and remained significantly above baseline for at least 20 minutes after antacid administration.

One antacid tablet and 5 ml of liquid antacid had similar effects, with peak pH levels of 5.24 and 4.79, respectively; these peaks were not significantly different ($P = 0.60$). Times to peak pH were six minutes and two minutes, respectively. The intragastric pH remained above 3.5 for 25 minutes with one tablet and for 40 minutes with 5 ml of liquid; pH values exceeded baseline values for approximately 60 minutes with either tablet or liquid antacids (Figure 1). The rate of

Table I. Baseline gastric samples fulfilling or failing study criteria for gastric acidity.

Participant Status	No. of Participants	Samples Qualifying* (No.)	Samples Failing No.	Samples Failing %
Qualified	15	103	28	21
Disqualified	8	26	36	58
Total	23	129	64	33

* Baseline pH ≤2.5 with intersample variation ≤0.5.

Table II. Mean (±SD) pH of gastric fluid aspirate at 0 to 240 minutes after administration of tablet or liquid antacid or placebo in ten fasted participants.

Time (min)	Placebo	Tablet ×1	Tablet ×2	Liquid 5 ml	Liquid 10 ml	*P*
0	1.72 ± 0.34[a*]	1.76 ± 0.39[a]	1.63 ± 0.29[a]	1.77 ± 0.41[a]	1.74 ± 0.25[a]	0.904
2	1.82 ± 0.32[c]	3.26 ± 2.13[bc]	2.75 ± 2.18[c]	4.79 ± 2.18[ab]	5.53 ± 1.36[a]	0.002
4	2.01 ± 0.67[c]	4.16 ± 1.92[b]	4.79 ± 1.99[b]	4.20 ± 2.46[b]	6.65 ± 0.76[a]	0.001
6	2.29 ± 1.48[b]	5.24 ± 1.73[a]	4.68 ± 2.23[a]	4.81 ± 2.27[a]	6.64 ± 0.84[a]	0.001
8	2.01 ± 0.78[b]	4.95 ± 1.93[a]	4.75 ± 2.11[a]	4.42 ± 1.95[a]	6.32 ± 0.89[a]	0.001
10	1.90 ± 0.41[b]	5.04 ± 1.93[a]	4.51 ± 1.60[a]	4.46 ± 2.17[a]	5.86 ± 1.17[a]	0.001
15	1.81 ± 0.50[c]	4.38 ± 2.06[ab]	3.15 ± 0.99[bc]	4.33 ± 2.26[ab]	5.15 ± 1.76[a]	0.001
20	1.76 ± 0.37[b]	3.69 ± 2.07[a]	2.73 ± 0.99[ab]	4.06 ± 2.38[a]	4.26 ± 1.96[a]	0.012
25	1.64 ± 0.33[b]	3.69 ± 2.04[a]	2.37 ± 1.08[b]	3.86 ± 2.53[a]	3.93 ± 2.17[a]	0.021
30	1.68 ± 0.35[b]	3.16 ± 1.87[ab]	2.21 ± 0.59[ab]	3.73 ± 2.57[ab]	3.95 ± 2.13[a]	0.022
35	1.62 ± 0.32[a]	2.86 ± 1.55[a]	2.48 ± 1.11[a]	3.62 ± 2.47[a]	3.56 ± 2.02[a]	0.060
40	1.57 ± 0.27[b]	2.55 ± 0.83[ab]	2.67 ± 1.84[ab]	3.81 ± 2.42[a]	3.54 ± 1.96[ab]	0.034
45	1.61 ± 0.33[a]	2.82 ± 1.75[a]	2.65 ± 1.88[a]	3.16 ± 2.15[a]	3.20 ± 1.62[a]	0.219
50	1.65 ± 0.42[a]	2.42 ± 1.39[a]	2.13 ± 0.74[a]	3.23 ± 2.06[a]	2.86 ± 1.58[a]	0.108
55	1.60 ± 0.34[a]	2.32 ± 1.49[a]	1.96 ± 0.69[a]	2.92 ± 2.00[a]	3.38 ± 1.86[a]	0.055
60	1.75 ± 0.34[a]	2.40 ± 1.68[a]	1.89 ± 0.68[a]	2.53 ± 1.81[a]	3.33 ± 1.78[a]	0.111
70	2.14 ± 1.56[a]	2.36 ± 1.48[a]	2.00 ± 1.24[a]	2.66 ± 2.05[a]	2.93 ± 1.95[a]	0.734
80	1.92 ± 0.78[a]	2.38 ± 1.34[a]	1.74 ± 0.59[a]	2.69 ± 2.23[a]	2.67 ± 1.83[a]	0.496
90	1.84 ± 0.66[a]	2.17 ± 0.99[a]	1.64 ± 0.46[a]	2.58 ± 1.68[a]	2.76 ± 2.03[a]	0.282
100	1.56 ± 0.29[a]	1.94 ± 0.80[a]	1.64 ± 0.42[a]	2.24 ± 1.70[a]	2.53 ± 1.76[a]	0.322

			[illegible]	[illegible] — 1.95	0.32 ± 0.89[a]	0.001
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25	1.64 ± 0.33[b]	3.69 ± 2.04[a]	2.37 ± 1.08[b]	3.86 ± 2.53[a]	3.93 ± 2.17[a]	0.021
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60	1.75 ± 0.34[a]	2.40 ± 1.68[a]	1.89 ± 0.68[a]	2.53 ± 1.81[a]	3.33 ± 1.78[a]	0.111
70	2.14 ± 1.56[a]	2.36 ± 1.48[a]	2.00 ± 1.24[a]	2.66 ± 2.05[a]	2.93 ± 1.95[a]	0.734
80	1.92 ± 0.78[a]	2.38 ± 1.34[a]	1.74 ± 0.59[a]	2.69 ± 2.23[a]	2.67 ± 1.83[a]	0.496
90	1.84 ± 0.66[a]	2.17 ± 0.99[a]	1.64 ± 0.46[a]	2.58 ± 1.68[a]	2.76 ± 2.03[a]	0.282
100	1.56 ± 0.29[a]	1.94 ± 0.80[a]	1.64 ± 0.42[a]	2.24 ± 1.70[a]	2.53 ± 1.76[a]	0.322
110	1.69 ± 0.38[a]	2.18 ± 1.47[a]	1.61 ± 0.47[a]	2.20 ± 1.69[a]	2.39 ± 1.72[a]	0.590
120	2.21 ± 1.63[a]	1.86 ± 0.64[a]	1.82 ± 0.90[a]	1.91 ± 0.53[a]	2.12 ± 1.38[a]	0.915
150	2.70 ± 2.07[a]	1.88 ± 0.49[a]	1.54 ± 0.25[a]	2.31 ± 1.38[a]	1.87 ± 0.73[a]	0.237
180	2.18 ± 1.24[a]	1.93 ± 0.90[a]	1.60 ± 0.34[a]	1.80 ± 0.59[a]	1.77 ± 0.34[a]	0.539
240	1.45 ± 0.34[a]	2.34 ± 2.15[a]	1.44 ± 0.21[a]	2.03 ± 0.85[a]	1.77 ± 0.40[a]	0.450
SD†	2.07	1.64	2.63	2.09	1.11	

* Within each row, values followed by the same letter (eg, a . . . a, b . . . b, or c . . . c) are not significantly different at the 5% level for Newman-Keul's multiple comparison test.[13]

† The amount of difference needed within each column for any two means to be significantly different.

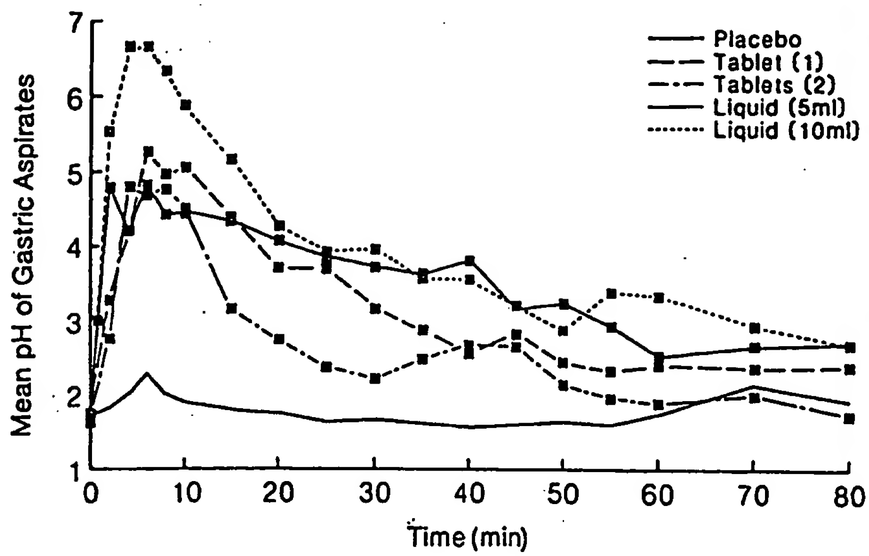


Figure 1. Mean pH levels from gastric fluid aspirated from 0 to 80 minutes after administration of tablet or liquid antacid or placebo in 10 fasting subjects.

decline in pH after peak levels was similar for one tablet and 5 ml of liquid.

In contrast, at the higher doses, significant differences between the tablets and the liquid were apparent. Although both produced peak pH values at four minutes, peak pH was 6.65 after 10 ml of liquid and 4.79 after two tablets. Between two and eight minutes, the gastric pH was significantly higher after administration of 10 ml of liquid than two tablets. The gastric pH was maintained above 3.5 for 40 minutes with 10 ml of liquid, whereas the pH dropped below 3.5 within 15 minutes after ingestion of two tablets. In the group treated with 10 ml of liquid, intragastric pH remained above baseline values for at least 1.8 minutes, whereas in the group treated with two experimental tablets, the pH returned to baseline values by approximately 80 minutes.

The mean pH of gastric aspirates was significantly higher after 10 ml of liquid than after 5 ml of liquid at 2, 4, 6, 8, and 20 minutes. No significant differences were found between the one-tablet and two-tablet doses.

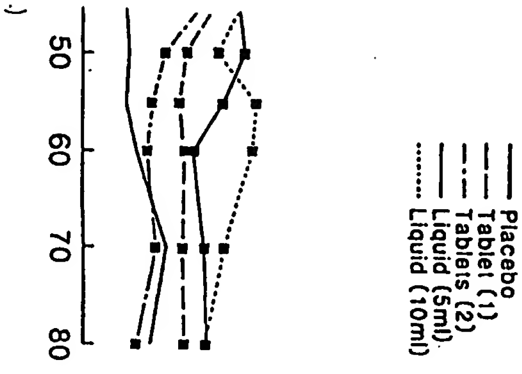
Effect of Antacids Given One Hour After a Standard Meal

There were no significant differences in baseline pH between the five treatment groups (Table III). When the subjects were fed, the gastric fluid pH rose to peak levels from 2.88 to 3.29 in 15 to 30 minutes.

After antacid administration, the mean gastric pH rose but was not significantly different from the pH in the placebo group (Figure 2). The mean pH after administration of 10 ml of liquid antacid

Table III. Mean (±SD) pH of gastric fluid aspirate at 0 to 240 minutes after administration of tablet or liquid antacid or placebo in ten fed participants.

Time (min)	Placebo	Tablet		Liquid		P
		X1	X2	5 ml	10 ml	
0	1.85 ± 0.25[a]	1.70 ± 0.25[a]	1.91 ± 0.36[a]	1.76 ± 0.29[a]	1.65 ± 0.26[a]	0.251
15	3.00 ± 0.72[a]	3.20 ± 0.38[a]	3.33 ± 1.44[a]	2.79 ± 0.97[a]	3.29 ± 0.44[a]	0.632
30	3.21 ± 0.85[a]	2.85 ± 0.80[a]	2.97 ± 1.03[a]	2.89 ± 0.77[a]	3.23 ± 0.71[a]	0.765
45	2.79 ± 1.15[a]	2.46 ± 0.80[a]	2.92 ± 1.02[a]	2.61 ± 0.83[a]	3.34 ± 0.89[a]	0.302
60†	2.93 ± 1.41[a]	2.29 ± 0.90[a]	2.50 ± 0.90[a]	2.18 ± 0.68[a]	3.38 ± 0.87[a]	0.054
75	2.88 ± 1.64[a]	3.03 ± 0.68[a]	3.08 ± 0.92[a]	2.84 ± 1.22[a]	3.98 ± 1.29[a]	0.210
90	2.05 ± 0.59[c]	3.16 ± 0.85[a,b]	2.76 ± 0.76[a,b,c]	2.28 ± 0.66[b,c]	3.10 ± 1.11[a]	0.004



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·irated from 0 to 80 minutes after d or placebo in 10 fasting subjects.

ıc mean pH of gastric aspirates was ficantly higher after 10 ml of liquid after 5 ml of liquid at 2, 4, 6, 8, and ıinutes. No significant differences found between the one-tablet and ·ablet doses.

·t of Antacids Given One Hour · a Standard Meal

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ter antacid administration, the mean ic pH rose but was not significantly ·ent from the pH in the placebo ɔ (Figure 2). The mean pH after nistration of 10 ml of liquid antacid

Table III. Mean (±SD) pH of gastric fluid aspirate at 0 to 240 minutes after administration of tablet or liquid antacid or placebo in ten fed participants.

Time (min)	Placebo	Tablet ×1 (25mEq)	Tablet ×2 (51mEq)	Liquid 5 ml (28mEq)	Liquid 10 ml (57mEq)	P
0	1.85 ± 0.25[a]*	1.70 ± 0.25[a]	1.91 ± 0.36[a]	1.76 ± 0.29[a]	1.65 ± 0.26[a]	0.251
15	3.00 ± 0.72[a]	3.20 ± 0.38[a]	3.33 ± 1.44[a]	2.79 ± 0.97[a]	3.29 ± 0.44[a]	0.632
30	3.21 ± 0.85[a]	2.85 ± 0.80[a]	2.97 ± 1.03[a]	2.89 ± 0.77[a]	3.23 ± 0.71[a]	0.765
45	2.79 ± 1.15[a]	2.46 ± 0.80[a]	2.92 ± 1.02[a]	2.61 ± 0.83[a]	3.34 ± 0.89[a]	0.302
60†	2.93 ± 1.41[a]	2.29 ± 0.90[a]	2.50 ± 0.90[a]	2.18 ± 0.68[a]	3.38 ± 0.87[a]	0.054
75	2.88 ± 1.64[a]	3.03 ± 0.68[a]	3.08 ± 0.92[a]	2.84 ± 1.22[a]	3.98 ± 1.29[a]	0.210
90	2.05 ± 0.59[c]	3.16 ± 0.85[ab]	2.76 ± 0.76[abc]	2.28 ± 0.66[bc]	3.30 ± 1.11[a]	0.004
105	1.84 ± 0.44[a]	2.49 ± 1.03[a]	2.88 ± 1.08[a]	2.20 ± 0.51[a]	2.70 ± 0.94[a]	0.065
120	1.71 ± 0.32[a]	2.07 ± 0.60[a]	2.53 ± 0.99[a]	2.07 ± 1.03[a]	2.16 ± 0.61[a]	0.226
135	2.03 ± 1.29[a]	1.60 ± 0.30[a]	2.13 ± 0.55[a]	2.20 ± 1.54[a]	2.13 ± 0.70[a]	0.670
150	1.62 ± 0.48[a]	1.55 ± 0.25[a]	2.04 ± 0.44[a]	2.26 ± 1.79[a]	1.78 ± 0.44[a]	0.348
165	1.65 ± 0.59[a]	1.63 ± 0.33[a]	1.86 ± 0.37[a]	1.72 ± 0.46[a]	1.75 ± 0.37[a]	0.781
180	1.50 ± 0.27[b]	1.51 ± 0.36[b]	1.95 ± 0.49[a]	1.51 ± 0.25[b]	1.59 ± 0.25[b]	0.023
195	1.60 ± 0.31[a]	1.52 ± 0.31[a]	1.97 ± 0.54[a]	1.51 ± 0.24[a]	2.02 ± 1.54[a]	0.392
210	1.69 ± 0.49[a]	1.54 ± 0.34[a]	1.83 ± 0.44[a]	1.50 ± 0.27[a]	2.13 ± 1.72[a]	0.499
225	1.99 ± 0.85[a]	1.72 ± 0.73[a]	1.72 ± 0.34[a]	1.52 ± 0.20[a]	2.30 ± 1.62[a]	0.384
240	1.75 ± 0.30[a]	1.72 ± 0.53[a]	1.86 ± 0.53[a]	1.65 ± 0.37[a]	2.22 ± 1.54[a]	0.547
SD‡	0.81	1.06	1.12	1.35	1.09	

* Within each row, values followed by the same letter (eg. a . . . a, b . . . b, or c . . . c) are not significantly different at the 5% level for Newman-Keul's multiple comparison test.[13]

† Antacid or placebo administration was at 60 minutes after the meal.

‡ The amount of difference needed within each column for any two means to be significantly different.

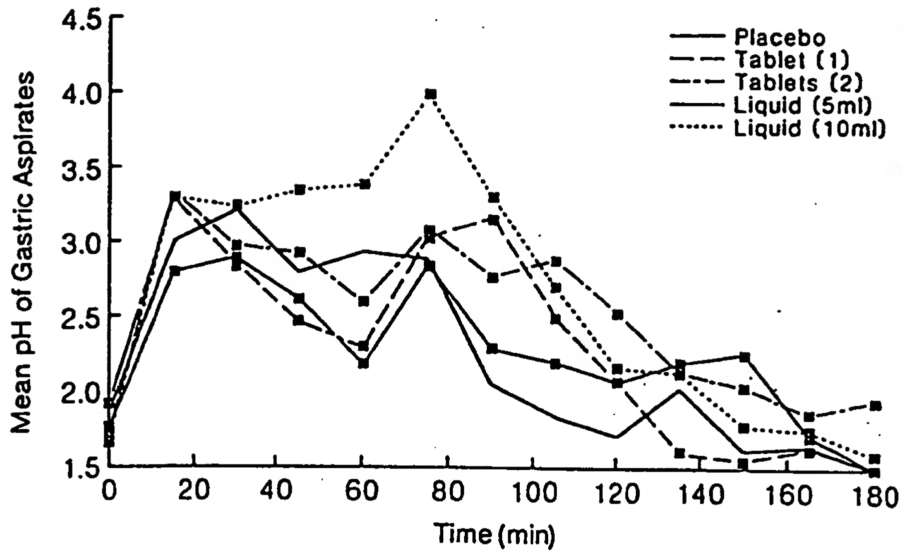

Figure 2. Mean pH levels from gastric fluid aspirated from 60 to 240 minutes after a standard meal in 10 fed subjects. Placebo or antacid was administered at 60 minutes.

was higher than in the other treatment groups, but this group also had a higher pH immediately before administration of medication, so that the net increase after antacid administration was not significantly different.

DISCUSSION

For this study, only subjects with baseline gastric pH of 2.5 or less in three consecutive samples and with variation between samples of less than 0.5 units were included. The incidence of higher baseline pH and variability in acid content was unexpectedly high among the volunteers enrolled in the study: 64 of 193 gastric aspirate samples taken at baseline had pH values greater than 2.5, for a failure rate of 33%. Even more surprising was the unusually high pH in the majority of cases in which the person was disqualified, whether for the day or for the entire study. Of the 64 baseline samples that did not meet the criteria, 56 (88%) were associated with pH readings greater than 6. The pH in the stomach is generally believed to be between 1.0 and 3.5, and more commonly between 1.0 and 2.5,[6] and it is unusual to find anacidity in such a large proportion of healthy young adults.

Eight volunteers failed to achieve the required baseline readings in 58% of samples and were disqualified from the study. For the 15 subjects who completed at least one part of the study, 21% of baseline pH levels did not meet the criteria. The ages, weights, and proportions of men and women completing at least one part of the study were similar to those of the total group screened and

thus the qualifying participants w representative sample of the total g

Because antacid tablets are more table and generally more palatable antacid liquids, they tend to be acceptable to patients. A more prolo reduction of gastric acidity has reported with a tablet formulation with a liquid formulation.[14] The re of our study showed that in fa subjects one experimental antacid t and 5 ml of liquid antacid were eq effective in raising intragastric pH had a similar duration of antacid ef

Doubling the dose of liquid an produced a greater and longer la antacid effect. Although the prolo effect may be of therapeutic benefi magnitude of increase in pH may n so desirable. If the gastric conten ceeds pH 5, a physiological resp may cause secretion of acid, know "acid rebound."[15]

Another unexpected finding in study was the similarity of effect of and two experimental tablets. One planation may be that two tablets chewed or swallowed less thorou than one tablet, inasmuch as the ta were administered without water. An possibility is that clumping occurre the stomach when the ratio of antac gastric juice rose too high, limiting t vivo response. Because the antacid a ity for a tablet is directly related to surface area exposed to the reac

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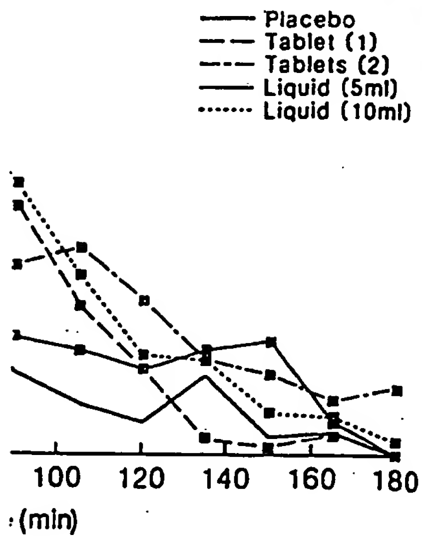

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ıe majority of cases in which the person ·as disqualified, whether for the day or ›r the entire study. Of the 64 baseline ımples that did not meet the criteria, 56 (89%) were associated with pH readings ·eater than 6. The pH in the stomach is :nerally believed to be between 1.0 and 5, and more commonly between 1.0 ıd 2.5,[6] and it is unusual to find anacidity such a large proportion of healthy ›ung adults.

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thus the qualifying participants were a representative sample of the total group.

Because antacid tablets are more portable and generally more palatable than antacid liquids, they tend to be more acceptable to patients. A more prolonged reduction of gastric acidity has been reported with a tablet formulation than with a liquid formulation.[14] The results of our study showed that in fasting subjects one experimental antacid tablet and 5 ml of liquid antacid were equally effective in raising intragastric pH and had a similar duration of antacid effect.

Doubling the dose of liquid antacid produced a greater and longer lasting antacid effect. Although the prolonged effect may be of therapeutic benefit, the magnitude of increase in pH may not be so desirable. If the gastric content exceeds pH 5, a physiological response may cause secretion of acid, known as "acid rebound."[15]

Another unexpected finding in our study was the similarity of effect of one and two experimental tablets. One explanation may be that two tablets were chewed or swallowed less thoroughly than one tablet, inasmuch as the tablets were administered without water. Another possibility is that clumping occurred in the stomach when the ratio of antacid to gastric juice rose too high, limiting the in vivo response. Because the antacid activity for a tablet is directly related to the surface area exposed to the reaction medium[11] and antacid tablets often do not disintegrate in the stomach,[15] the efficacy of the tablets may have been compromised if they were not chewed sufficiently to create a suspension of antacid particles.[8] It seems unlikely that reactivity of the antacid, once in suspension, would have been a problem unless the material reaggregated in the stomach. The experimental formulation showed high ANC in vitro. The finding of white clumps in the gastric aspirate of some participants up to 30 minutes after administration of tablets supports the possibility that the subjects failed to chew the tablets completely or that clumping subsequently occurred in the stomach.

Our results in fed patients indicated only a minor elevation of intragastric pH after antacid administration in either formulation or dose. The presence of food may have hindered the reactivity of antacids with gastric acid.[10] A previous study[16] demonstrated reduced ANC of antacids in the presence of protein-rich food. This may be due to the loss of aluminum hydroxide, as aluminum ions react with phosphate ions, which are present in high concentrations in foods that contain protein. Moreover, in the presence of food, antacids can further stimulate acid secretion.[17] Thus the lack of significant antacid effects after a meal points to the importance of establishing a better antacid dosage schedule for patients with gastric hyperacidity.

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Long-Term Treatment
Hypertension with Ni

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ABSTRACT

The efficacy and safety of long-term
ment with oral nitrendipine were e
ated in 34 patients with essential ar
hypertension. Nitrendipine alone s
cantly lowered systolic and dia
blood pressure levels in 28 patients
completed the preliminary four-
dose-setting phase. Twenty-one pat
completed the one-year treatment. E
pressure control was maintained by n
dipine alone in 11 patients. Ten pat
not adequately controlled at the e
the dose-setting phase were success
treated with nitrendipine combined
acebutolol or muzolimine. It is concl
that nitrendipine is a promising calc
antagonist for the treatment of art
hypertension.

INTRODUCTION

The World Health Organization gu
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The New England
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IN VIVO AND IN VITRO EVALUATION OF LIQUID ANTACIDS

JOHN S. FORDTRAN, M.D., STEPHEN G. MORAWSKI, B.A., AND CHARLES T. RICHARDSON, M.D.

Abstract An in vivo test of the efficacy of liquid antacids given after a meal was shown to yield reproducible results. An average dose-response curve, obtained with the use of various doses of a single antacid, was different in subjects whose peak histamine response exceeded 25 mEq per hour and in those whose response was less than 16.6 mEq per hour. In individual subjects, however, the peak histamine response did not accurately predict the in vivo reduction in gastric acidity by antacid. Although the relative in vivo potency of equal volumes of four different antacids varied widely, this potency could be predicted with reasonable accuracy by means of an in vitro test, which showed the potency per milliliter of antacid to vary 17-fold among different commercial products.

These experiments indicate that when antacids are prescribed, dosage should be determined by the milliequivalents of neutralizing capacity rather than by an arbitrary volume or number of tablets of different antacids, that the variable responses of individual patients to antacids should be taken into account, and that the doses commonly used in the treatment of duodenal ulcer should be increased. (N Engl J Med 288:923-928, 1973)

IN 1966 we reported that calcium carbonate powder and liquid aluminum-magnesium hydroxide ingested one hour after a standard meal reduced gastric acidity for at least three hours,[1] whereas these and other antacids ingested in the fasting state reduced acidity for only about 30 minutes.[2] The present studies were designed to learn more about the action of antacids taken after a meal, which is the main time when these drugs are prescribed for treatment of peptic ulcer.

GENERAL METHODS

All subjects had chronic duodenal or gastric ulcer or peptic esophagitis. None had evidence of delayed gastric emptying on x-ray or clinical examination, and none had had a recent complication, such as bleeding or perforation. None were on anticholinergic therapy.

After a fast of 10 to 12 hours the patients were fed a standard meal consisting of 150 g of broiled ground meat, seasoned with salt and pepper, two pieces of toast with butter and 180 ml of water. Patients were studied on several different test days, during which different doses of a single antacid, or different antacids, or water as a control were ingested one hour after the meal.

At intervals after the meal a 16 Fr. tube was inserted into the stomach under fluoroscopic control. A sample of the gastric contents was removed and analyzed for hydrogen ion concentration by the method of Moore and Scarlata.[3] A Sargent pH meter and standards of pH 1.07, 2.1, 4.0 and 7.0 were used. Basal secretion of acid and the peak histamine response were determined by standard methods.

RESULTS

Gastric Acidity Measured Sequentially after a Meal with and without Antacid

Each of seven patients with duodenal ulcer, all with a peak histamine response exceeding 25 mEq of hydrochloric acid per hour, were studied on two test days. On one day each subject ingested 60 ml of water one hour after eating. On the other day 156 mEq* of aluminum-magnesium hydroxide in a volume of 60 ml (Maalox, W. H. Rorer) was ingested.

The results are shown in Figure 1. When water was taken after the meal, gastric acidity remained at relatively low levels for the first hour and a half, in spite of the fact that acid was presumably secreted at near maximal rates during this period.[4,5] The change from a slow to a rapid rate of increase in gastric acidity occurred at the time when gastric acidity was about 8 mEq per liter, and the pH about 2.2. The meal used in these studies buffered hydrochloric acid in vitro down to but not below a pH of 2.2.[5] These results suggest, therefore, that in spite of high rates of acid secretion, gastric acidity rises slowly until the meal's buffer (the part that is not emptied from the stomach) is fully titrated to pH 2.2. This effect required about 1½ hours in the seven subjects included in Figure 1. After that time acid secretion continues, presumably at a rapid rate,[5]

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*Milliequivalents of antacid is defined by the mEq of hydrochloric acid required to keep an antacid suspension at pH 3.0 for 2 hours in vitro.

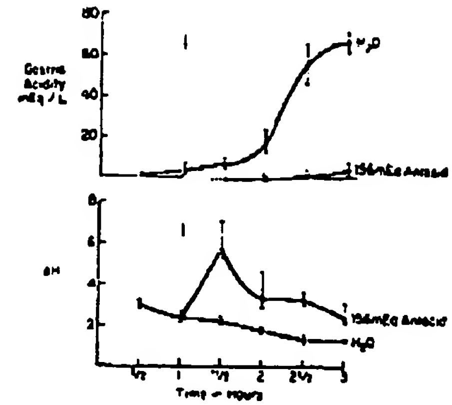

Figure 1. Gastric Acidity and pH in Response to a Meal when Either 156 mEq of Antacid or 60 Ml of Water Was Ingested (Arrows).

Results are means ± S.E. in seven patients with duodenal ulcer.

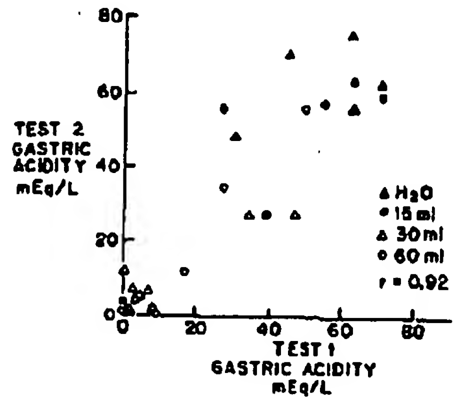

Figure 2. Reproducibility of Gastric Acidity Three Hours after the Standard Meal.

Individual subjects received the same amount of antacid on each day.

but since no unacidified protein (buffer) remains in the stomach, acidity rises rapidly, to an average maximum of 65 mEq per liter in our seven patients.

The striking effect on gastric acidity of ingesting 156 mEq of antacid is shown in Figure 1. Acidity was near zero for two hours after the antacid was ingested, rising to only about 3 mEq per liter by the end of the experiment. The pH of the gastric contents 30 minutes after the antacid was about 5.8, as compared to 2.2 at this interval when no antacid was ingested.

These results indicate that there are many ways in which antacid potency in vivo could be expressed, including the length of time the pH is higher than some arbitrary value, and the change in pH or the reduction of acidity at an arbitrary interval. In the results reported subsequently we have used the degree of reduction of gastric acidity two hours after antacids, compared to the level of acidity with water as a control, as a measure of antacid potency in vivo.

Reproducibility

Reproducibility was assessed in 30 patients by either water or the same dose of antacid given on two separate test days. The results are shown in Figure 2. Although variation from one test day to the next was observed, generally a good or poor response to a certain dose of antacid occurred on both test days in a given patient. The correlation coefficient was 0.92.

Dose-Response Relations

Average results. Figure 3 shows the average hydrogen ion concentration of the gastric contents three hours after the meal and two hours after various doses of liquid aluminum-magnesium hydroxide (Maalox, W. H. Rorer). The dose of antacid is expressed in terms of both milliliters of the liquid and milliequivalents of antacid as determined by in vitro titration to pH 3.0.

In 18 patients with duodenal ulcer whose peak histamine response was greater than 25 mEq per hour (range of 25 to 76 and average of 36.7), designated "hypersecretors" in Figure 3, the hydrogen ion concentration with no antacid was 49.9 mEq per liter. Increasing doses of antacid resulted in a progressive fall in gastric acidity. In this group of patients a dose of 30 ml (78 mEq) was required to reduce gastric acidity by approximately ½.

By contrast, in 11 patients with gastric ulcer or peptic esophagitis, whose peak histamine response was less than 16.6 mEq per hour (range of 5.7 to 16.6 and average of 9.1), designated "hyposecretors" in Figure 3, gastric acidity with no antacid was only 14.8 mEq per liter. A dose of approximately 9 ml (23 mEq) of antacid would be expected (by interpolation) to reduce acidity by ½. These results indicate that the average response of patients to antacid therapy is dependent on the parietal-cell mass, as estimated by the peak histamine response.

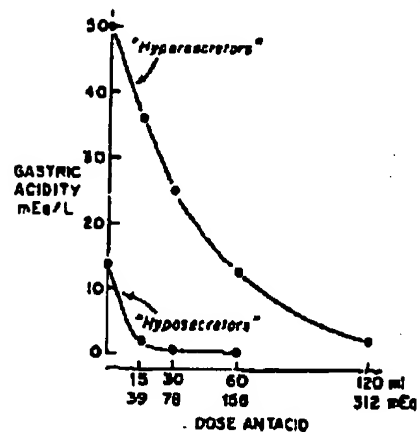

Figure 3. Antacid Dose-Response Curve (Maalox) in a Group of Patients Whose Peak Histamine Response Was Greater than 25 mEq per Hour ("Hypersecretors") and in a Group Whose Peak Histamine Response Was Less than 16.6 mEq per Hour ("Hyposecretors").

The description of antacid effectiveness in the previous paragraphs has been in terms of fractional or percentage reduction in acidity. The absolute reduction in average acidity with 15 ml (39 mEq) of antacid is approximately equal in the high and low secretors (13 mEq per liter in both groups), but the fractional reduction is much greater in the low secretors.

Individual results. Figure 4 shows the results in individual subjects, plotting the gastric acidity when no antacid was administered (horizontal axis) against the gastric acidity when either 15, 30 or 60 ml (39, 78 or 156 mEq) of antacid was given (vertical axis). Most patients whose gastric acidity was less than 40 mEq per liter without any antacid had at least a twofold reduction in gastric acidity by 15 ml of antacid. On the other hand, most patients whose gastric acidity without antacid was greater than 40 mEq per liter had relatively little reduction in gastric acidity by the 15-ml dose. (These results obviously apply to acidity only at the specified time of gastric sampling.) A fivefold reduction in gastric acidity for the high-secretor group was usually achieved only with the 60-ml dose of antacid. Approximately ½ of the high secretor group had a greater than 10-fold reduction in gastric acidity with the 60-ml dose of antacid.

The response of individual patients in fractional and absolute terms can be derived from Figure 4. No matter how the results are expressed, the response of individual patients to antacid therapy varies widely. For instance, some patients with the same level of acidity without antacid had very different degrees of reduction in acidity by the same dose of antacid.

In a total of 19 patients reasonable and convincing individual dose-response curves could be constructed, and from these the milliliters of antacid required to give a twofold and a fivefold reduction in gastric acidity was determined. The correlation coefficient of these values with the peak histamine response was 0.56 and 0.36, respectively, and wide scatter was evident. This finding indicates that the amount of antacid required to reduce gastric acidity twofold or fivefold in an individual patient correlates poorly with and cannot be predicted with accuracy from the peak histamine response. Therefore, the degree to which a given patient responds to antacids must depend not only on his parietal-cell mass but also on the rate at which he empties the antacid from the stomach, and on his gastric secretory response to eating.[6] Which of these factors varies in different patients, and thus accounts for the different response to antacid therapy, is not known.

The data were also examined to determine if the rate of basal secretion or the ratio of basal to peak secretion was of value in predicting the response to antacid therapy. All correlation coefficients were less than 0.24.

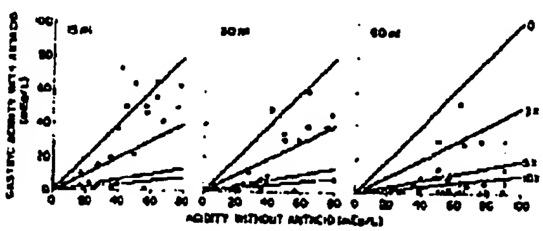

Figure 4. Gastric Acidity of Individual Patients after 15, 30 and 60 Ml (39, 78 and 156 mEq) of Aluminum-Magnesium Hydroxide (Maalox), Plotted against the Gastric Acidity when No Antacid Was Given.

Lines depicting zero reduction and reductions of two, five and 10 times in gastric acidity are shown. Open circles indicate patients with a peak histamine response of less than 16.6 mEq per hour, and closed circles those with a peak histamine response of greater than 25 mEq per hour. The closed triangles, plotted for the 60-ml dose only, are the results in patients described in other sections of this paper (i.e., they did not have a complete dose-response study).

Relative Potency of Different Liquid Preparations in Vivo

Sixty milliliters of water (as control) and 60 ml of Maalox (W. H. Rorer), Gelusil (Warner-Chilcott), Phosphaljel (Wyeth) and Camalox (W. H. Rorer) were compared in 11 patients, all of whom had a peak histamine response greater than 25 mEq per hour. The patients were tested on separate days with the different antacids, and the order of testing was randomized. The results are shown in Table 1. It is evident that the same volumes of these antacids have markedly different in vivo capacities to reduce gastric acidity. For instance, Phosphaljel diminished acidity hardly at all (as compared to the water control), whereas Camalox produced an 18-fold reduction.

The values in Table 1 apply only to the specific sampling time of two hours after the antacid (Three hours after eating, or two hours after antacid). However, in other, unpublished studies we have found that a similar qualitative conclusion would have been reached at sampling times of 30, 60 and 150 minutes, although with different absolute values for gastric acidity.

In Vitro Antacid Potency

Preliminary experiments were done at room temperature and at 37°C, in isotonic saline and in water, at different stirring rates, and with titration to different pH end points. Reaction temperature and the presence of sodium chloride in the test solution did not influence in vitro antacid potency or the relative effectiveness of different liquid antacids. However, the pH end point, the rate of stirring and whether or not the antacid was gently swirled after it was added to water or saline made an important difference in absolute and relative

Table 1. In Vivo Comparison of Four Antacids in 11 Patients with Duodenal Ulcer.*

Test Substance	Mean (H) ± SE
Water	68.8 ± 8
Phosphaljel	54.8 ± 9
Gelusil	29.4 ± 10
Maalox	7.6 ± 3
Camalox	3.8 ± 4

*60 ml of antacid given 1 hr after a meal; gastric acidity was measured 3 hr after the meal. When analyzed by paired analysis, each value is significantly different from the preceding value ($p<0.05$).

in vitro potency of different antacids. Rapid stirring greatly enhanced the effectiveness of some antacids, whereas for others it made little difference. Swirling gently before titration was begun made the in vitro test reproducible. If swirling was omitted, the antacid tended to flocculate, and in these cases, the results of triplicate testing varied markedly.

The final procedure selected was as follows: 1 ml of antacid was added to 100 ml of water at 37°C. The 250-ml Erlenmeyer flask was gently swirled three times to suspend the antacid evenly in the water. The mixture was then stirred at exactly 60 rpm, with the use of a magnetic stirrer and a 2.5-cm magnet. (This specific rate of stirring is obviously arbitrary; however, it was selected because it seemed more likely to simulate mixing conditions in the stomach than rapid agitation.) The pH of the mixture was measured, and 0.10 N hydrochloric acid was added from a buret at intervals (every five minutes for the first hour, and every 10 minutes for the next) over a two-hour period to lower the pH to 2.0, 2.5 or 3.0. Since acid was added only at the specified times, the pH in the intervals exceeded the end-point pH level. The test was repeated three times with each antacid, always with use of a new bottle, well shaken before opening. The results of repeat testing were virtually identical.

Figure 5 presents the in vitro results (end-point pH 3.0) with the four antacids used in the in vivo study previously described. Wide differences in the in vitro antacid potency of these antacids are evident. Figure 6 shows the correlation of the in vivo results (Table 1) with in vitro tests carried out at pH 2.0, 2.5 and 3.0. It is evident that the in vitro results at pH 3.0 correlate better with in vivo potency than in vitro tests at pH 2.0 or 2.5. For example, at pH 2.0 or 2.5 Phosphaljel appears as potent as Gelusil, which is contrary to their unequal potencies in vivo.

The agreement between one specific in vitro test, with titration to pH 3.0,* and the in vivo results was excellent, suggesting that this in vitro method may be used to predict in vivo activity of other liquid antacid preparations. (It is not known whether this in vitro method would accurately reflect in vivo activity of antacid tablets or powders.) For this reason, many liquid antacids, selected on the basis of availability in local stores, were titrated in vitro, with the results shown in Table 2. A wide range of activity is notable, 1 ml of Phosphaljel requiring only 4 ml of 0.1 N hydrochloric acid and 1 ml of Ducon requiring 70 ml of 0.1 N hydrochloric acid to maintain reaction pH at 3.0. The rate of reaction of antacid with hydrochloric acid and the antacid constituents of each preparation are also given in Table 2.

A second type of in vitro analysis was performed to determine the degree to which antacids elevate the pH of an acidified meal homogenate. The homogenized

*The choice of pH 3.0 as an end point for the in vitro test has no physiologic or pathological implications; it is simply the in vitro end point that empirically was found to correlate best with in vivo antacid potency.

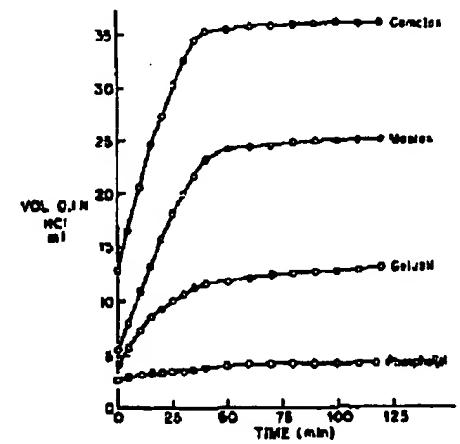

Figure 5. Titration of 1 Ml of Four Antacids with 0.1 N Hydrochloric Acid (HCl).
The pH end point was 3.0.

meal (steak, toast and butter, etc., as described above) was acidified to pH 2.0 by the addition of 1 N hydrochloric acid. Twenty-milliliter aliquots of the acidified meal were incubated at 37°C with 2.5 ml of antacid, with stirring at 60 rpm by a magnetic stirrer. The pH of the mixture after 30 minutes was read and recorded. The results, correlated with the in vivo experiments and with the in vitro titration of antacids to pH 3.0, are shown in Figure 7. The antacids varied widely in the degree to which the pH of the acidified meal was raised. However, ability to elevate the pH of the acidified meal toward pH 6 correlated well with the in vivo results with the four antacids so tested and with the in vitro titration to pH 3.0, with all antacids in this study.

Since the components of common antacids (aluminum hydroxide, magnesium hydroxide, magnesium trisilicate and calcium carbonate) vary widely in calculated antacid potency in vitro, it should be possible in principle to predict the relative in vitro potency of the various commercial antacids listed in Table 2 from their product labels. However, this is not true in practice because the amounts of each component are often

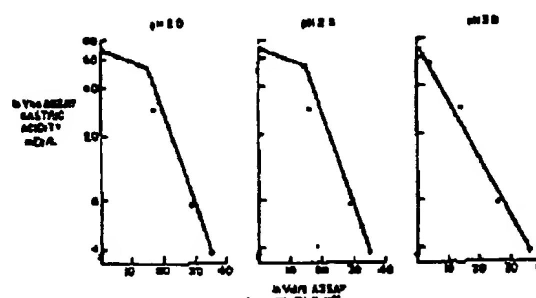

Figure 6. Comparison of In Vivo and In Vitro Potency of Water (Control) and Four Antacids.
Note that the vertical axis is a logarithmic scale. The in vivo data are also shown in Table 1, and the in vitro results in Figure 5.

Table 2. Titration to pH 3.0 of 1 Ml of Antacid with 0.1 N Hydrochloric Acid, 60 rpm, at 37°C.

Antacid	Ml of 0.1 N Hydrochloric Acid at 120 Min*	% of Final Volume Added at 0 Min	at 10 Min	at 30 Min	at 60 Min
Ducon	70.4	29	43	65	83
Mylanta II	41.4	10	20	42	67
Titralac	38.7	85	93	97	98
Camalox	35.9	49	80	91	99
[illegible]	28.1	23	44	88	99
Maalox	25.8	21	42	77	95
Creamalin	25.7	43	69	99	100
Di-Gel	24.5	23	50	93	98
Mylanta	23.8	17	30	66	90
Silain-Gel	23.1	14	29	61	87
Marblen	22.8	75	86	91	95
WinGel	22.5	37	58	87	91
Gelusil-M	22.3	49	80	89	94
Riopan	22.1	16	28	57	81
Amphojel	19.3	20	48	85	96
A-M-T	17.9	36	58	74	85
Kolantyl Gel	16.9	34	57	86	90
Trisogel	16.5	43	66	83	97
Malcogel	15.9	25	50	67	81
Gelusil	13.3	31	54	79	83
Robalate	11.3	30	61	92	95
Phosphaljel	4.2	59	68	90	93

*The value in this column, divided by 10, is a measure of buffer capacity of 1 ml of antacid in mEq after 120 min. this applies to the special circumstances of this in vitro test.

Aluminum hydroxide, aluminum phosphate, calcium carbonate, calcium hydroxide; magnesium carbonate; magnesium hydroxide; magnesium phosphate; magnesium trisilicate, glycine, methylamine; methyl cellulose; Bentyl & dihydroxyaluminum aminoacetate.

not specified by the manufacturer, and because the degrees of solubility ("reactivity") of different aluminum and magnesium bases vary. Nevertheless, previous workers have shown, by a variety of in vitro tests, that commercial antacids vary widely in potency,[6,7] and Littman observed that an in vitro test correlated with the duration of neutralization of the gastric contents by four aluminum hydroxide preparations in fasting patients.[8] Surprisingly enough, little clinical importance has been accorded to these results. Recent reviews, books and monographs discussing antacid therapy stress the point that there is little to choose between one liquid antacid and another; palatability, bowel habit, salt content and cost are the features of different antacids by which a choice of a specific drug has usually been recommended. Perhaps this attitude has developed because of the lack of evidence that in vitro potency reflects in vivo effectiveness under conditions in which antacids are actually used, and because in vitro tests can be carried out in so many different ways that almost any antacid can be made to appear relatively potent by some in vitro test. No matter what the reason, this belief is wrong. For instance, the neutralizing capacity of 15 ml of liquid antacid might vary from 6 to 105 mEq, and this in vitro difference is directly correlated with the degree to which antacids reduce acidity in patients.

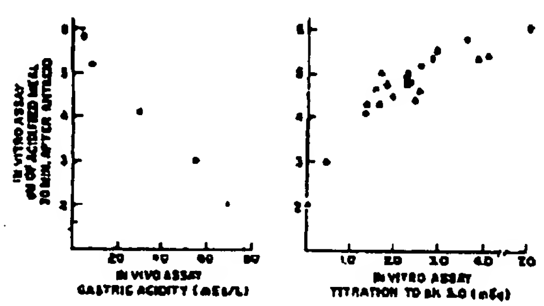

Figure 7. Ability of Different Antacids to Raise the pH of an Acidified Meal in Vitro.

The results are Plotted against the in vivo results (left side) and against the results of in vitro titration to pH 3.0 (right side). The closed triangles represent the effect of water as a nonantacid control, the closed circles are the four antacids tested in vivo (Table 1), and the open circles are the other antacids listed in Table 2.

Clinical Interpretation

Clinical interpretation of pharmacologic and physiologic studies such as these are hampered by lack of knowledge of the degree of neutralization necessary to heal an ulcer and to prevent recurrent peptic ulceration. In the past, many workers have assumed that antacids must reduce acidity to near zero (pH 3.5 or higher) to eliminate peptic activity. This concept was never verified or disproved experimentally, and to insist that reductions in acidity of lesser magnitude are clinically unimportant seems unjustified. It seems likely that the degree to which acidity must be reduced to heal and prevent peptic ulcer is variable in different patients, depending on the degree of mucosal resistance. Admittedly, there is no direct experimental proof of this hypothesis.

Recently, Goldberg and his co-workers conducted an experiment that bears on the degree that acidity must be reduced to prevent experimental esophagitis in the cat.[9] These workers found that cat esophagitis was markedly diminished as acidity was reduced from approximately 31 mEq per liter (pH 1.6) to 12 mEq per liter (pH 2.0), and that esophagitis was completely prevented if acidity was reduced to 6.1 mEq per liter (pH 2.3). These results were obtained even though all the test solutions contained the same amount of pepsin, and even though in vitro peptic activity (with hemoglobin as substrate) was equal and maximum over this range of acidity. Although these experiments of Goldberg et al. are not directly applicable to ulceration in the human stomach or duodenum, they suggest that reduction in gastric acidity to degrees that can easily be achieved clinically by the use of antacids might favorably influence the course of peptic ulceration in patients. Furthermore, in an older study, antacid therapy was found to reduce the frequency of Mann-Williamson ulcers in dogs even though gastric acid was incompletely neutralized.[10]

Even if it turns out that antacids are of no value in speeding healing in peptic ulcer and are useful only for relieving pain, it makes sense to use them in the most

effective way possible. Bonney and Pickering[11] showed that pain did not occur in patients with duodenal ulcer unless the pH of gastric contents was less than 2.0.

Several conclusions from the present set of experiments seem justified. The first is that different liquid antacids vary markedly in their in vivo and in vitro potency, and this fact should be taken into account when antacid drugs are prescribed. Therefore, it seems preferable to judge antacid dosage according to milliequivalents of neutralizing capacity rather than volume or number of tablets of the different antacids. Otherwise, patients will be receiving quite different amounts of antacid, depending on the specific preparation and whether a tablet or liquid is used. On the other hand, potency is not the only factor that should be considered in the choice of an antacid. Cost, taste, salt content, bowel habit, underlying diseases other than peptic ulcer and side effects are also important. The listing of antacids in order of potency in Table 2 does not imply the same order of clinical value. For instance, we are concerned about hypercalcemia and falling creatinine clearance in patients treated with large amounts of calcium carbonate.[12] Furthermore, two studies have suggested that calcium carbonate gives poorer clinical results than other antacids,[12,13] possibly because of calcium-induced gastric hypersecretion.[14,15] Whether the amount of calcium in commercial liquid preparations is an advantage because of increased potency per unit volume antacid, or a disadvantage because of the reasons listed above, has not been definitely settled. At present it seems to us best to avoid these antacids and to obtain the desired potency by a higher volume of noncalcium-containing antacids.

Secondly, the response of individual patients to antacids varies widely and cannot be predicted from measurements of acid secretion. Some patients have a marked reduction in gastric acidity with small amounts of antacid whereas others have a poor response to large amounts of antacid. It seems feasible and advisable to assess the response to antacids in the clinical management of selected patients. Individual variability should also be taken into account in any double-blind controlled studies of antacid effectiveness.

Thirdly, the commonly recommended doses of antacid for treatment of duodenal ulcer are much too low. For instance, a fivefold reduction in acidity for two hours in a patient with duodenal ulcer would require 156 mEq of antacid in most patients (Fig. 4). From the data in Table 2 it may be seen that this amount is equivalent to from 371 to 22 ml, depending on the antacid selected. Most physicians use 15 ml (one tablespoonful) regardless of which antacid is prescribed. In all but a few cases, this figure would fall far short of the dose required to produce a fivefold reduction in gastric acidity two hours after taking the antacid.

We are indebted to Lottie Isaacks and Martha Irvin for technical assistance in carrying out the in vivo tests, and to Dr. Morton Grossman for criticisms of these results.

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United States Court of Appeals for the Federal Circuit

03-1339

THE ARNOLD PARTNERSHIP,

Plaintiff-Appellant,

v.

Jon Dudas, Acting Under Secretary of Commerce for Intellectual Property and Acting Director, Patent and Trademark Office, and NICHOLAS P. GODICI, Commissioner for Patents,

Defendants-Appellees.

Christopher N. Sipes, Covington & Burling, of Washington, DC, argued for plaintiff-appellant.

Linda Moncys Isacson, Associate Solicitor, Office of the Solicitor, United States Patent and Trademark Office, of Arlington, Virginia, argued for defendants-appellees. With her on the brief were John M. Whealan, Solicitor; and Raymond T. Chen, Associate Solicitor.

Donald O. Beers, Arnold & Porter, of Washington, DC, for amicus curiae GlaxoSmithKline. With him on the brief was David E. Korn. Of counsel on the brief was Scott A. Chambers, Patton Boggs, LLP, of McLean, Virginia.

Appealed from: United States District Court for the Eastern District of Virginia

Judge Leonie M. Brinkema